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New Reproductive Technologies and the Health Care System:

The Case for Evidence-Based Medicine

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Royal Commission on
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New Reproductive Technologies and the Health Care System: The Case for Evidence-Based Medicine

Volume 11 of the
Research Studies

Royal Commission on
New Reproductive Technologies

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Consistent with the Commission's commitment to full equality between men and women, care has been taken throughout this volume to use gender-neutral language wherever possible.



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Preface from the Chairperson



As Canadians living in the last decade of the twentieth century, we face unprecedented choices about procreation. Our responses to those choices — as individuals and as a society — say much about what we value and what our priorities are. Some technologies, such as those for assisted reproduction, are unlikely to become a common means of having a family — although the number of children born as a result of these techniques is greater than the number of infants placed for adoption in Canada. Others, such as ultrasound during pregnancy, are already generally accepted, and half of all pregnant women aged 35 and over undergo prenatal diagnostic procedures. Still other technologies, such as fetal tissue research, have little to do with reproduction as such, but may be of benefit to people suffering from diseases such as Parkinson's; they raise important ethical issues in the use and handling of reproductive tissues.

It is clear that opportunities for technological intervention raise issues that affect all of society; in addition, access to the technologies depends on the existence of public structures and policies to provide them. The values and priorities of society, as expressed through its institutions, laws, and funding arrangements, will affect individual options and choices.

As Canadians became more aware of these technologies throughout the 1980s, there was a growing awareness that there was an unacceptably large gap between the rapid pace of technological change and the policy development needed to guide decisions about whether and how to use such powerful technologies. There was also a realization of how little reliable information was available to make the needed policy decisions. In addition, many of the attitudes and assumptions underlying the way in which technologies were being developed and made available did not reflect the profound changes that have been transforming Canada in recent decades. Individual cases were being dealt with in isolation, and often in the absence of informed social consensus. At the same time, Canadians were looking

more critically at the role of science and technology in their lives in general, becoming more aware of their limited capacity to solve society's problems.

These concerns came together in the creation of the Royal Commission on New Reproductive Technologies. The Commission was established by the federal government in October 1989, with a wide-ranging and complex mandate. It is important to understand that the Commission was asked to consider the technologies' impact not only on society, but also on specific groups in society, particularly women and children. It was asked to consider not only the technologies' scientific and medical aspects, but also their ethical, legal, social, economic, and health implications. Its mandate was extensive, as it was directed to examine not only current developments in the area of new reproductive technologies, but also potential ones; not only techniques related to assisted conception, but also those of prenatal diagnosis; not only the condition of infertility, but also its causes and prevention; not only applications of technology, but also research, particularly embryo and fetal tissue research.

The appointment of a Royal Commission provided an opportunity to collect much-needed information, to foster public awareness and public debate, and to provide a principled framework for Canadian public policy on the use or restriction of these technologies.

The Commission set three broad goals for its work: to provide direction for public policy by making sound, practical, and principled recommendations; to leave a legacy of increased knowledge to benefit Canadian and international experience with new reproductive technologies; and to enhance public awareness and understanding of the issues surrounding new reproductive technologies to facilitate public participation in determining the future of the technologies and their place in Canadian society.

To fulfil these goals, the Commission held extensive public consultations, including private sessions for people with personal experiences of the technologies that they did not want to discuss in a public forum, and it developed an interdisciplinary research program to ensure that its recommendations would be informed by rigorous and wide-ranging research. In fact, the Commission published some of that research in advance of the Final Report to assist those working in the field of reproductive health and new reproductive technologies and to help inform the public.

The results of the research program are presented in these volumes. In all, the Commission developed and gathered an enormous body of information and analysis on which to base its recommendations, much of it available in Canada for the first time. This solid base of research findings helped to clarify the issues and produce practical and useful recommendations based on reliable data about the reality of the situation, not on speculation.

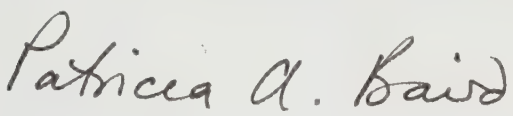
The Commission sought the involvement of the most qualified researchers to help develop its research projects. In total, more than 300

scholars and academics representing more than 70 disciplines — including the social sciences, humanities, medicine, genetics, life sciences, law, ethics, philosophy, and theology — at some 21 Canadian universities and 13 hospitals, clinics, and other institutions were involved in the research program.

The Commission was committed to a research process with high standards and a protocol that included internal and external peer review for content and methodology, first at the design stage and later at the report stage. Authors were asked to respond to these reviews, and the process resulted in the achievement of a high standard of work. The protocol was completed before the publication of the studies in this series of research volumes. Researchers using human subjects were required to comply with appropriate ethical review standards.

These volumes of research studies reflect the Commission's wide mandate. We believe the findings and analysis contained in these volumes will be useful for many people, both in this country and elsewhere.

Along with the other Commissioners, I would like to take this opportunity to extend my appreciation and thanks to the researchers and external reviewers who have given tremendous amounts of time and thought to the Commission. I would also like to acknowledge the entire Commission staff for their hard work, dedication, and commitment over the life of the Commission. Finally, I would like to thank the more than 40 000 Canadians who were involved in the many facets of the Commission's work. Their contribution has been invaluable.



Patricia Baird, M.D., C.M., FRCPC, F.C.C.M.G.

Introduction



The importance of the health care system to Canadians is abundantly clear; it is a symbol of strongly held Canadian values, reflecting the fact that we believe individuals should be treated equally in the face of disease or injury. It is also clear that Canadians place great value on having children and that they consider it important to provide treatments that may facilitate this. The Commission was faced with the task of reconciling the need to provide help to people who are infertile with the need to manage the health care system responsibly, given the many legitimate claims on its resources.

The path the Commission chose toward this reconciliation was the concept of evidence-based medicine — that is, the idea that medical practice and management of the health care system should be based on knowledge gained from appropriate evaluation of treatments and their results. Evidence-based medicine is one of the considerations Commissioners kept in mind when making decisions about new reproductive technologies, the others being an ethical framework (outlined in Volume 1) and an understanding of Canadian social values and attitudes (outlined in Volume 2).

Since having children is important to Canadians, effective and safe means of helping people who would otherwise be childless to have children should be included in our health care system if such means exist. A key phrase, however, is "effective and safe." It is important, therefore, to ask: do infertility treatments work and what are the risks of short- or long-term harms to either the woman or the children she may have? As is the case with many other medical treatments, however, answers to these questions are not always clear; attempts at answering them for specific categories of treatment have often been poorly designed, based on samples that were too small for meaningful results or not comparable with other studies. The Commission set out to analyze the information available in the

international literature in order to provide some answers to these questions. The results of these analyses are presented in this volume.

The volume begins with two studies that show the need for health care decision making to be based on empirical evidence that can come only from a comprehensive program of technology assessment. The studies that follow assess the technologies that are used in treating various categories of infertility. The volume concludes with two studies that outline how information about the long-term effectiveness and safety of the treatments could be generated; they describe how a record-linkage approach, using existing health and other records, could allow assessment of long-term outcomes while at the same time respecting the need to protect privacy.

The studies in this volume are important in their own right, providing the best information available at the time they were completed on the effectiveness of various treatments for particular categories of infertility. Their collective impact, however, is far greater than the sum of their parts. Taken together, these studies provide compelling support for the usefulness of the concept of evidence-based medicine. It is important to realize that it is applicable not just to the field of new reproductive technologies but to the health care system as a whole. If evidence-based decisions are made about new reproductive technologies, they avoid being part of the problem, in the sense of overburdening or undermining the system, and become part of the solution, by contributing to the system's capacity to deliver effective health care services in a fair, rational, and cost-effective way.

The Studies

Michael Rachlis's paper on Canada's health care system illustrates the need to change the current approach to health care. He paints a picture of a system that is overloaded and underled, one in which the federal government is cutting back its financial contributions and several provinces are in breach of the Canada Health Act, the legislation that embodies the principles upon which health care in Canada is based. He documents a substantial amount of inappropriate care delivered to patients by doctors and other health care providers, partly because of a lack of quality assurance. He criticizes the lack of a clear process for determining standards of practice, the lack of a definition of what constitutes a "medically necessary" service under the Canada Health Act, and the existence of significant barriers to funding health promotion or prevention programs.

While Dr. Rachlis supports the implementation of quality assurance programs as a means of improving the quality of health care, he points out that, in times of financial constraint, it can be difficult to find new resources for evaluation and better clinical management. His consideration of quality assurance is important, however, because it provides a blueprint for moving health care from a focus on inputs to a focus on potentially useful examinations of outcomes.

The analysis by Arminée Kazanjian and Karen Cardiff reinforces Dr. Rachlis's finding that decisions on health care funding of new technologies have been made in a partisan, fragmented, and ad hoc manner. They see a need for technology evaluation that takes into account the social context within which technology develops, and economic, legal/ethical, and political components. To help meet this need, they develop a model for health technology decision making that they then appraise in light of the international literature on health care decision making. On the basis of a review of more than 1 300 abstracts and a detailed analysis of 173 directly relevant articles, they find that the key factors in their model are consistent with the trends identified in the scientific and medical literature. They also find that there is a shortage of empirically based work that would help determine how decisions regarding public policy should be made to better serve the public interest.

Given the Commission's timeframe and the size of the data set that would be needed, it was not possible to set up and carry out the randomized clinical trials that could determine the effectiveness of given treatments by specific indications. It was possible, however, to assess the available data from all published clinical studies in this area worldwide, and this in itself is a major contribution. A technique called meta-analysis may allow aggregation of individually conducted studies. These studies may not be adequate in themselves to reveal treatment effects, but, when aggregated according to certain criteria, may provide useful information. This is the subject of the next four studies.

In the first study, Patrick Vandekerckhove and colleagues searched more than 41 journals over a period of 14 years for data on infertility treatments. Their findings demonstrate that, while there have been increases in the number of randomized controlled studies in recent years, infertility treatments generally have *not* been characterized by effective use of evidence to evaluate outcomes. The authors call for multicentre cooperative research as a means of gaining the needed evidence.

Edward Hughes and colleagues focussed on studies of the effectiveness of infertility treatments for unexplained infertility and for endometriosis, and of the effectiveness of *in vitro* fertilization (IVF) for different indications. Their findings present a bleak picture, both in terms of the paucity of well-designed and executed randomized trials in these areas and in terms of the evidence the existing trials provide on the effectiveness of the technologies. The authors were able to find only one trial of IVF versus no treatment, a critical comparison because of the fact that couples may become pregnant without any intervention. It is necessary to know how many babies would have been born without treatment, in order to know how many were born because of the treatment. A control group having no treatment is, therefore, essential. Few of the other trials or cohort studies that the authors include were of sufficient quality or size, even when pooled, to provide any reliable evidence of the effectiveness of the treatments for specific indications. In addition, the

authors found that very few studies provide information on the live birth rate, which is the category of greatest relevance for policy makers and individuals considering the treatment. Most studies include only clinical pregnancy as an indicator of success, without including, for instance, the rate of spontaneous abortion.

The technologies assessed by Dr. Hughes and colleagues are all intended to treat female infertility. A substantial proportion of infertility, however, is due to male infertility or to a combination of male and female infertility. In their second study, Patrick Vandekerckhove and colleagues use the techniques of meta-analysis to assess the effectiveness of treatments for male infertility, with disappointing results. In spite of intensive efforts, few good randomized trials could be found through on-line and manual searches of the literature. There is not enough evidence to prove whether any treatment is effective. The authors are able, however, to differentiate between promising and less promising treatments, and this may provide guidance for future research efforts. This guidance is needed, as newer treatments for male infertility, such as micro-injection of sperm, which were not included because their use is too recent, have not been evaluated as required. By the end of 1993, fewer than 200 infants had been born following micro-injection, indicating that it cannot yet be viewed as a safe and proven treatment.

Effectiveness is but part of the equation in evaluating infertility treatments, the other being safety. John Jarrell, Judy Seidel, and Philip Bigelow have also applied the techniques of meta-analysis to evaluate what, if any, adverse health effects are associated with drugs used for ovulation induction. The two most commonly used of these are clomiphene citrate and human menopausal gonadotropin (hMG). As is the case with effectiveness studies, there is a dearth of good studies on the health effects of ovulation induction drugs. The authors identified nearly 5 000 references in the literature, of which only 937 met the authors' criteria; few of these were of high enough quality to include in meta-analysis, and even fewer used randomized methods or included a non-treatment comparison group. The authors' finding that there has been little specific interest in documenting whether these drugs, despite their widespread use, have adverse effects in humans is of concern. It is clear from their study that more and better data are required on outcomes so that the frequency of any adverse effects can be assessed. Women considering using these drugs need to know about the known risks, as well as about the limits of the available information on risk, in order to give informed consent to treatment.

Chedoke-McMaster Hospital in Hamilton, Ontario, has one of the few IVF programs the Commission is aware of that has conducted a comprehensive program review. The next three papers, by Ron Goeree, Roberta Labelle, and John Jarrell, deal with specific aspects of the review: the methodological challenges inherent in such a review; the cost-effectiveness of IVF compared with that of other infertility treatments; and

the perceptions of a small public sample concerning an IVF program and its effect on patients' quality of life.

The authors' experience with attempting to evaluate a technology that is already widely available leads them to stress the importance of proper technology evaluation *before* a treatment is disseminated. In this case, IVF was already publicly funded on the basis of anecdotal "evidence" of its efficacy; this meant that a true randomized trial was not possible, because those seeking and eligible for treatment would not consent to be randomized. The solution the authors devised, a quasi-randomized trial whereby the experimental group received treatment right away and the control group was assigned to a six-month waiting list rather than having no treatment at all, brought additional challenges. These included limits on the number of cycles that could be observed with the experimental group, delays in scheduling treatment for them, and a sizable proportion of drop-outs, particularly in the control group. The authors underscore the importance of timing in the evaluation of a new technology that is subject to refinement and modification, and in which the expertise of people involved in administering the treatment is developing.

The authors propose three possible objectives for Ontario's IVF program — to produce pregnancies, to improve patients' quality of life, and to produce pregnancies *and* to increase patients quality of life — and conclude, based on their program review, that none of these objectives are being met. Further, a sample of 80 members of the local community rated IVF as one of the least necessary of a list of 12 medical programs. It is hard to accurately assess the importance placed on IVF by the general public because most people know they are fertile since they already have children and are unlikely to place high priority on a program they know they don't personally need. Nevertheless, their findings lead the authors to question whether the Ontario government should continue to finance IVF in the same way as it does now.

Taken together, these three papers provide a perspective on the unique requirements of conducting randomized trials of infertility treatments and further underscore the need for evidence-based medicine to be instituted as a way of ensuring that treatments provided through the health care system are effective.

Assessing a technology for effectiveness and safety before it is widely disseminated is one of the facets of evidence-based medicine; another is ongoing monitoring to determine long-term health outcomes for recipients, and, in the case of infertility treatments, for their children. Following specific individuals over a period of years is expensive, time-consuming, and invasive of their privacy, but there is another approach that may be more cost-effective and that does not intrude on the lives of individuals. Ways of using record linkage to track long-term health outcomes are explored in the last two studies in this volume.

In the first, Lynda Hayward, Darlene Flett, and Christine Davis investigate and catalogue existing data bases that could be used to link

records on parents' infertility diagnosis and treatment with records pertaining to their children's health. In the second, Carl D'Arcy, Nigel Rawson, and Lindsay Edouard have conducted a feasibility study on how a particular group of data sets held in one province could be used to study outcomes. They outline how health records in Saskatchewan could be used to track infertile individuals, their partners, and children over a specified period of time to evaluate the frequency of adverse health outcomes and to compare these outcomes to those in a comparison group of people who are not infertile. They chose to use Saskatchewan because of its universal drug plan, which means that anybody who is prescribed fertility drugs, whether alone or as part of other infertility treatments, in Saskatchewan or out of province, can be identified. Both studies conclude that record linkage, as a technique, is undervalued and that it should be recognized as a much-needed instrument to track long-term outcomes of infertility treatments and thus provide information that is not currently available on the long-term effects of treatment for the women and children involved.

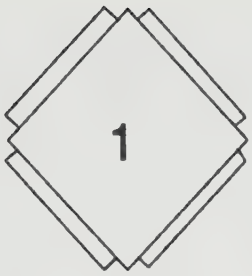
Conclusion

Two over-riding conclusions emerge from a careful reading of the studies in this volume. The first is that the quality of existing research on the effectiveness of infertility treatments is such that it is incapable of providing the information that is needed in this area. This is particularly unsettling given the length of time that some treatments, such as fertility drugs, have been available. The second is that decisions in the field of infertility treatment, and, by extension, in the health care system as a whole, are being made in the absence of any systematic examination of treatment outcomes.

The poor state of evidence-based medicine documented in the meta-analyses in this volume becomes more understandable if viewed against the backdrop of the papers by Dr. Rachlis, Dr. Kazanjian and Ms. Cardiff, and Mr. Goeree and colleagues. This does not, however, make the situation acceptable, and the very existence of the other papers in this volume are proof that this situation does not need to continue. The concepts of quality assurance and technology evaluation are known and available to practitioners and policy makers alike. In the absence of sufficient numbers of individual, large, randomized controlled trials, meta-analysis, as a methodology, may be able to provide answers to questions about the effectiveness and safety of specific infertility treatments. The analysis of the McMaster IVF program shows that, while it has limitations and difficulties, it is possible to provide and analyze useful outcome data on infertility programs. In addition, the record-linkage approach described and the data bases catalogued show that it would be possible to use existing data to monitor adverse outcomes.

Increasing the attention given to treatment outcomes is an approach not limited to infertility treatments; it should also be applied to many other

areas of the health care system in Canada. In fact, the challenges facing both the infertility treatment community and the health care system as a whole are much the same: how to ensure that treatment and funding decisions are made on the basis of adequate evidence of both effectiveness and safety. Practitioners and policy makers need to make a commitment to the tenets of evidence-based medicine as part of the task of ensuring that the health care system continues to be a viable and valued part of Canada's social fabric.



The Canadian Health Care System

Michael M. Rachlis



Executive Summary

New Developments in Canadian Health Policy

Recent federal and provincial reports have concurred on two major conclusions about health policy. First, the health care system isn't nearly as important for the public's health as Canadians have come to believe. Second, the health care system is beset with a number of structural inefficiencies.

The public still believes, however, that doctors and hospitals are the most important factor affecting their health. The public also believes that the health care system is operated by doctors and administrators in an efficient fashion. Some provinces are attempting to develop broad social strategies for health while controlling the costs of health care.

Provincial governments find themselves in conflict with the public and the providers of health services. The public has different values and perceptions, and doctors and hospitals have conflicting interests.

If the Royal Commission wishes to see resources allocated to the prevention of infertility and the promotion of reproductive health, it will have to make these points as specific recommendations with details for implementation.

Reviews of health care demonstrate a substantial amount of inappropriate care delivered to patients by doctors and other health care providers. This problem is partly a result of fee-for-service as the

This paper was completed for the Royal Commission on New Reproductive Technologies in March 1992.

principal mode of physician payment and partly a result of a lack of quality assurance. In addition, doctors are poor communicators and often incorrectly elicit patients' preferences for tests and treatments.

The implementation of quality assurance programs can improve the quality of health care. In times of financial constraint, however, it has proved very difficult to find new resources for evaluation and better clinical management.

It is not clear which professional organization or government has responsibility for elaborating clinical standards for reproductive health care. The responsibility for monitoring and enforcing these standards is also not clear.

If the Royal Commission wishes to see better standard setting, evaluation (including technology assessment), and quality assurance, it will have to make these points as specific recommendations with details for implementation.

Changing Federal-Provincial Arrangements for Health Care

It is not completely clear which level of government has jurisdiction over health policy. However, the federal government is cutting back its financial contribution to the provinces for health care and its overall leadership for health policy. Health and Welfare Canada has made recent cuts to both family planning and sexually transmitted disease control.

The Canada Health Act is not being scrupulously enforced. Several provinces are in breach of the program criterion pertaining to accessibility because they have not passed appropriate legislation for negotiation with their physicians. Quebec is in breach of the portability criterion.

There are no clear rules in the Canada Health Act about which services should be funded. There is no process outlined in the act for determining which services should be provided. The Canada Health Act requires provinces to cover those services that are "medically required" or "medically necessary." However, no province or territory has defined these terms operationally. The provinces make their decisions about which services to fund without due process.

There is a leadership vacuum for the development of a national strategy for reproductive health. If the Royal Commission wishes to see a national strategy for reproductive health or effective national regulation of reproductive technologies, it will have to make these points as specific recommendations, with details for their implementation.

Recommendations

This section outlines three recommendations and then discusses the problem of the external costs of private *in vitro* fertilization (IVF) clinics.

1. There is no clear process for determining standards of practice in the Canadian health care system. If the Royal Commission wishes to ensure that standards are elaborated, then it should convene a meeting with representatives from Health and Welfare Canada, provincial and territorial governments, provincial medical licensing

organizations, the Royal College of Physicians and Surgeons, the Canadian Medical Association, the Canadian Nurses Association, consumer organizations, and other relevant groups. The Royal Commission should use the conference to help it determine a process for standards elaboration, monitoring, and enforcement.

2. At present the provinces make decisions about which health services to publicly fund on an ad hoc basis. The Canada Health Act mandates the provinces to provide those services that are "medically necessary" or "medically required." However, no province or territory has operationally defined these terms. The Royal Commission should recommend a national conference of governments, health care providers, and consumers to discuss a due process for determining which health services should be publicly funded.

3. There are significant barriers that obstruct the funding of programs that promote health or prevent illness. If the Royal Commission wishes to ensure that new programs are funded, it will have to make specific recommendations in this regard.

How To Deal with the Externalities of *In Vitro* Fertilization

Professor Robert Evans of the University of British Columbia has defined an externality as follows:

> One person or organization's behaviour may affect others, independent of any voluntary transaction. My playing of loud music at night disturbs your sleep; my refusal to be immunized increases your chances of getting polio; my failure to wear seat belts increases your taxes to pay my hospital bills. Conversely my beautiful garden not only gives you pleasure, but raises your property value. In so far as my behaviour fails to take account of such effects, because others have no way to induce me to respond to their preferences, I will (from a society-wide perspective) over-(under) indulge in activities with negative (positive) externalities.

If IVF services were not fully paid for by the public purse (as is the case in nine provinces and both territories), there would still be external costs imposed on the public system. There would be at least two types of externalities to privately funded IVF.

First, there might be medical complications associated with the procedures (e.g., laparoscopy) and drugs used for IVF. In the rare event that a woman suffered a heart attack while having an IVF procedure and was left brain dead on a respirator, the publicly funded health care system would be left to pick up costs of the treatment. In this example there might also be significant social welfare costs involved for the care of any children she might have previously adopted or borne. In fact, one might argue that the private system could not operate without the public system as a "back-up."

Second, there are increased costs associated with many of the children who are conceived through IVF. Because more than one

embryo is typically implanted during a cycle of IVF, the frequency of multiple births from IVF therapy is much higher than from births resulting from natural conception. As a consequence of these multiple births, there are more Caesarian sections, more premature deliveries, more low birthweight (< 2 500 grams) and very low birthweight (< 1 500 grams) babies, all resulting in increased health care and social costs.

Furthermore, there are long-term sequelae of prematurity and low birthweight. A number of studies have shown that these children are much more likely than those of normal birthweight to suffer from major and more subtle physical and psychological disturbances.

There are many different methods to deal with this situation. Following are three that might be used:

1. ***Do nothing***
   This would result in the external costs of IVF being borne by the public sector.

2. ***Providers pay a licence fee***
   If a regulatory agency were created (as in the United Kingdom), clinics could be required to pay an annual licensing fee. The fee could be established to meet the true costs of collecting data from the facility, administering the licensing agency, and paying for the externalities of IVF therapy.

3. ***Infertile women (couples) pay a special fee to the government for each IVF cycle***
   An actuarially-sound fee could be calculated for each cycle of IVF and the woman (couple) would pay this fee to the provincial ministry of health. It should be possible to calculate the costs associated with the implantation of one, two, or three or more embryos, and the fee could vary according to the number implanted.

Option #1 is used for cosmetic plastic surgery. These procedures (with few exceptions) are not covered by public health insurance. However, they do inevitably engender complications (even with the most proficient practitioners), which result in the consumption of publicly funded health care services.

On the other hand, IVF is somewhat different because there are potential complications to the children as well as the mother (the primary patient). Furthermore, the major complications for children relate to multiple pregnancies which are a result of couples' and physicians' attempts to maximize the success of the procedure. Therefore, it could be argued, that the success of a commercial operation is dependent upon a publicly funded health care system. This would support the concept of a fee levied on the facility. This could vary according to the average number of embryos implanted.

Introduction

This report provides an overview of the Canadian health care system. The first section identifies key concepts in health policy. Key participants in the health care system are identified in the second section. The third section analyzes the issues and trends affecting the health care system that relate to the mandate of the Commission. The fourth section outlines the major conclusions. Recommendations for further action by the Royal Commission are set out in the fifth section.

Key Concepts

This section defines certain terms and outlines the organization and financing of the health care system in Canada.

Definitions

Health

The World Health Organization (WHO) defined health in 1948 as "complete physical, mental and social well-being."[1] Over the past four decades, however, there has been a gradual separation of the concepts of well-being and health. Health is now seen as a resource for *achieving* well-being. This is reflected in the 1986 WHO definition:

> Health is the extent to which an individual or group is able, on the one hand, to realize aspirations and satisfy needs; and, on the other hand, to change or cope with the environment. Health is therefore seen as a resource for everyday life, not the objective of living; it is a positive concept emphasizing social and personal resources, as well as physical capacity.

Some provinces have gone further. For example, the Ontario Premier's Council on Health, Well-Being, and Social Justice outlined a vision for health:

> We see an Ontario in which people live longer in good health, and disease and disability are progressively reduced. We see people empowered to realize their full health potential through a safe, non-violent environment, adequate income, housing, food and education, and a valued role to play in family, work and the community. We see people having equitable access to affordable and appropriate health services regardless of geography, income, age, gender or cultural background. Finally, we see everyone working together to achieve better health for all.[2]

Disease Prevention

There are three levels of prevention. Primary prevention aims to prevent illness before there are clinical signs and symptoms. For example, the use of a condom for intercourse would prevent a woman from acquiring a sexually transmitted disease that could lead to infertility. Secondary prevention aims to prevent illness before there has been damage to the body. For example, a doctor could test a woman (and treat her) for sexually transmitted disease before her fallopian tubes become infected and damaged. Tertiary prevention aims to prevent further damage once disease has occurred. There is little difference between tertiary prevention and treatment.

Health Promotion

The WHO defined health promotion as follows: The process of enabling people to increase control over, and to improve, their health. It represents a mediating strategy between people and their environments, synthesizing personal choice and social responsibility in health to create a healthier future.[3]

The Organization and Financing of Health Care in Canada

History

The Constitution Act, 1867 has generally been interpreted as giving the provinces responsibility for health care. Section 92(7) of the act states:

> In each Province the Legislature may exclusively make Laws in relation to Matters coming within the Classes of Subjects next herein-after enumerated; that is to say, ...
> (7) The Establishment, Maintenance, and Management of Hospitals, Asylums, Charities, and Eleemosynary Institutions in and for the Province, other than Marine Hospitals.

The constitutional division of powers will be analyzed in more detail in a subsequent section. In fact, the constitutional division of powers for health policy is not clear.

The federal government proposed that it should take over more responsibility for health care in 1945, but this was rejected by the provinces. However, the federal government subsequently used its greater revenue-raising powers to develop a national health care program. In 1948, the federal government instituted the National Health Grants Program, which provided cost-shared funds to the provinces for the construction of hospitals.[4] In 1957, the federal government passed the Hospital Insurance and Diagnostic Services Act (HIDS) which paid one-half the cost of hospital insurance programs if the provinces met certain terms and conditions. In 1966, the federal government passed the Medical Care Act which paid one-half the cost of the provinces' medical insurance program if the provinces met certain terms and conditions. These so-called national standards for medicare were subsequently incorporated in the Canada Health Act in 1984:

1. public administration of the health insurance plan;
2. comprehensiveness of service;
3. universality of coverage (i.e., coverage of all residents of the province);
4. portability of benefits; and
5. accessibility of service and reasonable compensation of providers.

All provinces had joined the federal plan by 1971. Although the program was generally judged to be a success, there were problems. Some provinces were concerned that federal money was available for hospital and medical care only, when evidence was accumulating that many services were delivered more efficiently out-of-hospital by non-physician personnel. The federal government was concerned that it had no control over its expenditures because they were committed to paying one-half of the bills the provinces submitted.

In 1977, the federal government passed the Established Programs Financing Act[5] which converted the federal payment into tax points and a cash transfer. The federal government decreased its personal income tax rate by 13.5 percent and its corporate rate by 1 percent. This action allowed the provinces to increase their tax rates by these amounts without increasing the overall tax bill. In return, the federal government no longer paid one-half of the bills the provinces submitted. Rather, the federal contribution (the calculated value of the sum of the tax points and the cash transfer) was established at 50 percent of the cost of the programs in the base year (1975-76) and then was to grow at a rate commensurate with the growth of the economy (gross national product [GNP]) and population.

In 1984, the federal government passed the Canada Health Act, which subsumed the Hospital Insurance and Diagnostic Services Act and Medical Care Act. It provided more detail on the national standards for medicare and the provincial legislation necessary for provinces to receive a full federal contribution. The Canada Health Act detailed specific penalties for breaches of the accessibility criterion but not the others. The act allowed the federal government to reduce its cash transfers under the Established Programs Financing Act by the amount of user charges levied in a province. It also allowed the federal government to apply more general penalties if a province was assessed as breaching one of the other national standards. (There is more about the details of the mechanism for federal withholding in the third section of this paper.)

The federal government made the first change in the funding formula for the Established Programs Financing Act when it subjected the federal contribution for post-secondary education to the same temporary growth restrictions as other programs in the "6 & 5" restraint program in 1983-84 and 1984-85.

Since its election in 1984, the present federal government has made three structural changes in the formula for the federal contribution under the Established Programs Financing (EPF) Act:

- Bill C-96 was passed in 1986. It decreased the growth in the federal contribution under the Established Programs Financing Act (EPF) to *2 percent less than the growth in GNP*;
- Bill C-69 was passed by the House of Commons in June 1990. It froze the federal contribution for 1990-91 and 1991-92 and then decrease the growth in the federal contribution under EPF to *3 percent less than the growth in GNP*;[6] and
- Bill C-20 was passed in the fall of 1991. It extended the freeze on the federal contribution under EPF for three years (to make five years in total). The federal contribution continued to grow with the population (approximately 1 percent per year).

Notwithstanding that the tax points transferred in 1977 have grown in value commensurate with growth in the economy as a whole, the value of the federal contribution has diminished since 1983. The federal government calculates its cash transfers by subtracting the value of the tax points from its estimated contribution under the EPF. The cash transfers have been diminishing in real value since 1986. At some point in the future the federal government will not transfer any cash to the provinces. The exact timing depends upon assumptions about growth in the economy and the population, but it has been estimated that the province of Quebec will receive no more federal cash by 1995. Ontario will receive no more cash by 1998, and no province or territory will receive cash transfers under the EPF by 2002.

There was a danger that the federal government would no longer be able to enforce the Canada Health Act when it ceased to transfer cash to the provinces. However, Bill C-20 allows the federal government to withhold other transfer payments (e.g., under the Canada Assistance Plan) if the provinces breach the program criteria in the Canada Health Act.

Health Care Service Organization

There isn't actually a health care *system*. Most of the links between health care providers are informal. Most health care services are provided by autonomous doctors and hospitals. Most doctors are self-employed and practise by themselves or in small groups. Some physicians are employed by hospitals, universities, industry, or community health centres.

Most hospitals are private, non-profit corporations. Some hospitals are owned by the federal government (e.g., the Department of National Defence) or provincial governments (e.g., psychiatric hospitals). Some are owned by religious orders or municipalities. Most hospitals are funded on the basis of a global budget, which is usually based on the history of the hospital's budgets rather than any assessment of need. Health care services are also provided by nursing homes and other long-term care institutions, community health centres, occupational health clinics, nursing stations (particularly in the north and on Indian reserves), public health units, and home care programs.

There is no uniform definition of a community health centre (CHC). However, most employ non-physician personnel and have community (lay) boards. The physicians are usually paid a salary rather than a fee-for-service. CHCs usually have a broad view of the health needs of their communities and are often involved in advocacy on social and environmental issues. Quebec has more than 160 such centres, known as CLSCs (centres locaux de services communautaires). Ontario has 41, with 30 more in various stages of development. Saskatchewan and Manitoba have about half a dozen each, and there are small numbers in most other provinces.

Public health units are typically administered by local municipalities but may be run provincially. Some public health units run family planning and prenatal clinics, and many others run home care programs.

Some Canadian health clinics are run according to the principles of feminist health care. The women's health clinic in Winnipeg has been in existence for approximately 12 years. The staff operates as a collective, and every attempt is made to involve consumers as active participants in their own care and the governance of the centre. Other women's clinics are linked with hospitals or more traditional clinics or offer a limited range of services (e.g., only family planning or counselling).

Most reproductive services[7] are provided by doctors in private practice. Until the mid-1970s family doctors, rather than specialist obstetricians, assisted women in more than half of all deliveries. This proportion had dropped to 31 percent by the mid-1980s.[8] The usual reasons given for this phenomenon include the relatively low payment (fee per time worked) for obstetrical services, the encroachment on personal life of providing obstetrical care, and the increase in malpractice premiums for obstetrical care. As the number of deliveries by family doctors declined, obstetricians increased their share of deliveries. More recently, the use of midwives to provide prenatal care and assist in deliveries has gained momentum in some parts of the country. Ontario has passed legislation to regulate the practice of midwifery, and Quebec and Alberta are contemplating such a move.

Prenatal diagnostic services, such as amniocentesis and chorionic villus sampling (CVS), are usually provided at university teaching hospitals. Ultrasound is usually provided through private doctors' offices or free-standing imaging facilities.

Most infertility investigation and therapy is provided by private, self-employed physicians. More obstetrician/gynecologists are specializing in this area of practice. *In vitro* fertilization services are provided mainly at university teaching hospitals, but there are some private, free-standing IVF clinics.

Regulation

The regulation of the health care system is primarily at the provincial level but there is some overlap with the federal government. The provinces are responsible for licensing health professionals and facilities. The provinces directly determine licensing standards for all hospitals and are responsible for their inspection.

In each province, special legislation establishes the licensing bodies for physicians, nurses, and other health professionals. Provinces differ somewhat on which professionals they license or certify. For example, Ontario has no licensing body for social workers, but other provinces have regulated social work. Typically, the provincial legislation establishes a self-regulating body, which in turn establishes licensing standards for the profession. In Ontario and the western provinces the physician organizations are known as Colleges of Physicians and Surgeons. There is a fair bit of uniformity in licensing standards from province to province. There is much more variation in the ongoing monitoring of physicians and other health professionals.[9]

The federal government is responsible for the legislation that established the Royal College of Physicians and Surgeons in 1929. This law, requested by the Canadian Medical Association (CMA), was aimed at standardizing the requirements for medical specialties across the country.[10] The Royal College is a self-governing body that establishes the criteria (training and examinations) for the certification of specialists. This certification is accepted by all provinces except Quebec, which has established its own certification system.

Other federal regulations are administered through Health and Welfare Canada's Health Protection Branch, which is responsible for regulating drugs and medical devices.

The Canadian Council on Health Facilities is a voluntary, non-statutory organization that certifies hospitals and long-term care institutions.

Financing

The federal contribution to health care (tax points plus cash) covered approximately 45 percent of provincial expenditures on health care in 1979-80 but only 37 percent as of 1988-89. This proportion will decline more quickly because of the federal government's cuts to the funding formula.

The provinces raise most of their money for health care from general revenues. Quebec, Ontario, and Manitoba also levy payroll taxes to support health care. Alberta and British Columbia charge their residents premiums for health insurance.

Most physicians are in private practice and are paid on a fee-for-service basis. Physicians submit claims (either on cards or electronically) to the provincial health insurance plan and are typically paid within two to eight weeks.

Most hospitals receive a global budget from the provinces, usually based on the history of the hospital's budgets rather than any formal assessment of need. Alberta is moving to pay its hospitals on the basis of the severity of illness and need for care of its patients. One payment will be made to the hospital for each patient admitted. The payment will depend upon the patient fitting one of several hundred categories of case mix groups. Ontario is paying a small percentage of each hospital's budget on the basis of case mix now.

The province provides capital funds for non-profit institutions, with some institutional fund-raising usually required. The province is responsible for approving capital expenditures, especially those that will engender increases in operating expenditures. If institutions purchase new capital equipment (e.g., a CAT scanner) without authorization, the province may not pay for its operation.

Payment for other health care services is much more variable across the country. Public health services are typically funded through a combination of local and provincial sources. Community health centres are usually funded by provincial governments, mainly on global budgets.[11] Home care services are available unevenly across the country, funded from combinations of federal, provincial, local, and voluntary sources.

Provincial drug plans are also quite variable. Four provinces (British Columbia, Alberta, Saskatchewan, and Manitoba) have universal plans covering all residents. Newfoundland provides public coverage for seniors and social assistance recipients only. The other provinces provide coverage for seniors, those on social assistance, and at least one other group. British Columbia covers the drugs used for IVF, while Ontario does not.

There is also considerable variation in the benefits of private drug plans.[12] A sizable majority of the population has coverage from either public or private insurance plans. Private drug plans typically pay for only six cycles of IVF.

A feature of the payment mechanisms for health services is that the provincial budget for physicians is typically open-ended, while the budgets of the other services are fixed. Until the last decade, provincial ministries of health routinely paid the operating deficits (if any) of hospitals. In fact, the accumulated deficit was usually added to the base for the establishment of the next year's budget. Recently, however, the provinces have been tougher in their negotiations with hospitals.

Also until very recently, the provinces and the medical associations negotiated only the schedule of medical fees, not the total funds allocated to the physicians' budget.[13] It is now generally believed that there is no natural limit to medical expenditures.[14] Total medical expenses are a factor of the average fee charged, the number of physicians, the population (and its health status), and the number of medical services per capita. The costs of physicians' services can increase, therefore, as a result of an increase in the average fee claimed,[15] an increase in physician supply, an increase in

population (or decrease in its health status), or an increase in the number of medical services consumed per capita.

On the other hand, in Quebec there have been separate budgets for general practitioners' fees and various specialties since 1976. In Quebec and most other provinces, however, the budget for medical services may still rise in response to physician supply.[16] In Canada the physician supply has been growing at two to three times the rate of population increase since the early 1970s.

Most of the funding for health services goes to institutions and medical services. Table 1 shows the distribution of expenditures for various services in Canada in 1990.

As most reproductive services are provided by doctors in private practice, including infertility investigation and therapy, the principal mode of payment for them is fee-for-service.

Table 1. Allocation of Health Care Resources in Canada, 1990

Program Area	$ Millions	%
Hospitals, other institutions, and capital expenditures	32 567	52.8
Medical doctors	9 412	15.2
Other health professionals	4 332	7.0
Drugs (prescribed and non-prescribed)	8 238	13.3
Other	7 172	11.6

Source: Canada Health and Welfare Canada, Policy, Planning, and Information Branch, *Health Expenditures in Canada* (Ottawa: Minister of Supply and Services Canada, 1992).

Prenatal diagnostic services, including amniocentesis and CVS, are often provided through clinics at university teaching hospitals. The medical services may be paid by the province on a fee-for-service basis or through a hospital's or university's global budget. Most medical geneticists are on salary, but the procedures carried out by obstetricians involved in prenatal diagnosis are usually fee-for-service.

Only Ontario provides public funding for all IVF services, excluding drugs. Other provinces cover various combinations of infertility services.

Key Participants

Federal and National Organizations

Health and Welfare Canada

Health and Welfare Canada is responsible for the following:

- administration of the Canada Health Act;
- certain public health matters (e.g., safety of food and drugs);
- international health issues (including supervision and medical care at entries into Canada);
- provision of medical care to Aboriginal people and the people of the Yukon and Northwest Territories, as well as in federal facilities such as prisons;
- collection and publication of information relating to public health; and
- investigating and researching public health and welfare.

Other National Organizations

The Royal College of Physicians and Surgeons of Canada

The Royal College was created by statute in 1929 and is responsible for certifying medical specialists. It sets criteria for training and examinations. The federal legislation establishing the Royal College of Physicians and Surgeons includes as objects of the College:

> a. To further the excellence of professional training and the standards of practice in the various medical and surgical specialties in Canada; ... and
>
> c. To maintain a high standard of professional ethics, conduct and practice among medical and surgical specialties...

The Canadian Medical Association (CMA)

The CMA is the national professional organization for physicians. Members may join directly or through provincial affiliates. The CMA is built up of provincial associations that bargain directly for medical fees with their respective provincial governments. The CMA deals with national political issues for physicians and provides a forum for exchange of information between its provincial affiliates.

The Society of Obstetricians and Gynaecologists of Canada (SOGC)

The SOGC is a voluntary professional organization with approximately 900 active members. It is in the process of attempting to increase its membership from approximately one-third of Canadian obstetricians and gynaecologists. The Society has established guidelines for a number of procedures and services (e.g., Caesarian sections, diagnostic ultrasound). It has also published *Ethical Considerations of the New Reproductive Technologies* (with the Canadian Fertility and Andrology Society).

The Canadian Fertility and Andrology Society

The Society promotes study and research in the field of sterility, fertility, and andrology. Approximately one-third of the members are physicians and two-thirds are basic scientists. The Society established guidelines for therapeutic donor insemination in 1988.

The Canadian Voluntary Regulatory Association for Assisted Reproductive Technologies

This organization was formed in 1991 to establish standards for facilities that provide IVF. The Association would also like to collect uniform data on IVF, including long-term follow-up data on children, and to establish registries on donor insemination and intrauterine insemination. The organization is voluntary; membership is not a prerequisite for delivering IVF or other infertility services.

The Canadian Nurses Association (CNA)

The CNA is the national professional association for nursing in Canada. Its role is somewhat analogous to that of the CMA. The Quebec affiliate withdrew from the Association in 1985.

The Canadian Public Health Association (CPHA)

The CPHA is a voluntary association representing approximately 3 000 public health workers in Canada. It seeks improvement and maintenance of personal and community health through disease prevention and health promotion.

The Canadian Hospital Association (CHA)

The CHA is the national association for hospitals.

The Canadian Council on Health Facilities Accreditation (CCHFA)

The CCHFA is a voluntary association that accredits hospitals and long-term care institutions in Canada.

The Canadian Council of Health Service Executives (CCHSE)

The CCHSE is the professional association for health service managers in institutions and community settings. The CCHSE offers fellowships to encourage the development of high standards for health service management.

The Canadian Association of Social Workers (CASW)

The CASW is the national professional association for social workers. Social work is a regulated health profession in all provinces but Ontario.

The Health Action Lobby (HEAL)

The HEAL, formed in 1991, is a coalition of seven national health organizations: the CMA, the CNA, the CHA, the CPHA, the Canadian Long-Term Care Association, the Canadian Psychological Association, and the Consumers' Association of Canada. The HEAL is lobbying the federal government to maintain federal funding of health care and the national standards for health insurance found in the Canada Health Act.

The Canadian Health Coalition (CHC)

The CHC was formed in 1979 to protect and enhance medicare. The CHC encompasses more than 20 national health care organizations, unions, social non-governmental organizations, and consumer groups.

Provincial Organizations

Provincial Ministries of Health

Provincial ministries of health are typically responsible for:

- the regulation of health facilities and providers;
- administration of provincial medical insurance plans, including the medical and hospital insurance of provincial residents temporarily out of the province;
- the financing of health care facilities and other non-physician providers (e.g., community health centres, home care, community services); and
- the financing and, sometimes, the delivery of certain public health services (e.g., immunization, public health nursing, environmental and sanitary inspection).

Other Provincial Organizations

Provincial Physician Licensing Organizations

These organizations have different names in different provinces. In Ontario and the western provinces they are called Colleges of Physicians and Surgeons. (For convenience this section refers to the physician licensing organizations as "colleges.") These organizations are created by provincial statute and are responsible for licensing of physicians. Most of the statutes that created these organizations require the colleges to establish and maintain standards of practice. It is only within the last two decades, however, that the colleges have gradually moved toward the implementation of quality assurance programs. Quebec, Ontario, and British Columbia have programs in place that randomly select doctors for office audits. The colleges have different authority and governance from province to province.

Medical Professional Associations

These organizations have different names from province to province but they are usually called medical associations or medical societies. The organizations are non-statutory bodies that promote the profession's interest in their respective provinces. The medical associations are also responsible for negotiating medicare fees with provincial ministries of health.

Provincial Nursing Licensing Organizations

These organizations are usually called associations and combine the functions of a licensing body with those of a professional association, except in Ontario where the College of Nursing is responsible for licensing and the Registered Nursing Association of Ontario is responsible for professional matters.

Provincial Nursing Unions

Until the 1960s and 1970s, provincial nursing associations acted as the provincial negotiator for nurses. Since that time, however, the nurses' unions have split from the licensing bodies.

Provincial Hospital and Public Health Associations

These associations are the voluntary professional organizations for hospitals and public health departments.

The Conference of Deputy Ministers of Health

The Conference of Deputy Ministers of Health was created in 1973 as the successor to the Dominion Council on Health. The federal deputy minister of health and welfare chairs the conference, which is staffed by the intergovernmental and international branch of Health and Welfare Canada. The Conference has about 50 committees, subcommittees, and working groups. These include the Advisory Committee on Institutional and Medical Services, the Advisory Committee on Community Health, and the Committee on Health Human Resources.

Current Issues in Health Policy

Introduction

This section outlines the current major issues and trends in health policy. Since 1986, the federal government and seven of the provinces have released major reports or royal commission reports on health policy. In 1986, the federal government published *Achieving Health for All: A Framework for Health Promotion*, which outlined a new direction for achieving improvements in health in the population.[17] Since that time seven provinces (Ontario,[18] Quebec,[19] New Brunswick,[20] Nova Scotia,[21] Saskatchewan,[22] Alberta,[23] and British Columbia[24]) have received internal or commission reports regarding their health programs.

In 1991, the House of Commons Standing Committee on Health and Welfare, Social Affairs, Seniors, and the Status of Women issued its report, *The Health Care System in Canada and Its Funding: No Easy Solutions*.[25] The provincial reports reflect the federal report's conclusions and are described below. They have broad acceptance across provinces, political parties, legislatures, the academic community, and health organizations.

1. Health care services (especially doctor and hospital services) are less important for the population's health status than the public believes. When government considers how to spend the next dollar of public expenditure to improve the public's health, it appears that more resources devoted overall to hospitals and doctors are less likely to improve health status than if they were used for other government programs (e.g., income maintenance, housing, child care for disadvantaged groups).
2. In many provinces, expenditures on health care have been increasing at a greater rate than other government spending. From a payer's perspective, there appears to be an insatiable demand for health services. There is considerable evidence that the organization and financing of health care services lead to the delivery of considerable inappropriate care.[26]

Canadian governments therefore have two major health policy issues with which to grapple. They must strive to get the most improvement in health for their overall expenditures *and* to get the best effect for their health care dollar. The first issue argues for an overall strategy to improve the health of the population, while the second issue argues for a strategy to reform the health care system to enhance its effectiveness and efficiency.

This reflects a change in the thinking and values of government officials, academic researchers, and officials of health care organizations since the original debates about medicare in the 1950s and 1960s. Professor Jonathan Lomas of McMaster University has suggested, however, that the public still overestimates the importance of health care services and still believes that health care services are delivered in a cost-effective fashion. He claims that the public holds three values on health and health care:

1. medical care and hospital care are the major determinants of long-term improvements in health status;
2. resources in the health field are managed by hospitals and physicians only in response to population need; and
3. if providers respond only to need, and they require no assistance in the management of this response, then medicine must be a science that is practised with precision and devoid of discretion.[27]

In many ways the conflict in health policy lies between the different perceptions and values of the population, and of governments. There is also a basic conflict between the goals of government and the interests of the providers of health care services.

This section reviews current important issues in health policy, including the determinants of health, the development of strategies for health, inefficiencies within the health care system, quality assurance and technology assessment, the role of women as consumers in health care, and changing federal-provincial arrangements for health care.

Determinants of Health and the Development of Strategies for Health

Health Care and Health Status

Canadian health status improved markedly in the 50 years before the full implementation of medicare.[28] Between 1921 and 1971, infant mortality rates decreased from 74 to 16 per 1 000. Tuberculosis mortality fell from 70 to 3 per 100 000. Despite near-miraculous advancements in medical care, most of these improvements were attributable to improved public health services, broad societal trends (e.g., a falling birth rate), or other public policies (e.g., welfare, housing).[29] Even recent improvements in health status have resulted more from healthy public policies (e.g., anti-smoking legislation) than advances in the treatment of disease, substantial as these might have been.[30] The public perception persists, however, that these improvements in health are attributable to doctors, hospitals, and new drugs and other treatments.

There is relatively little public awareness of the broader determinants of health. In fact, there is much known about the causes of illness and the promotion of health. In its Ottawa Charter for Health Promotion, the WHO observes:

> The fundamental conditions and resources for health are peace, shelter, education, food, income, a stable eco-system, sustainable resources, social justice and equity. Improvement in health requires a secure foundation in these basic prerequisites.[31]

The Ontario Premier's Council on Health Strategy[32] recently reviewed the evidence on the determinants of health and concluded that there is strong evidence to support the assertion that social and economic conditions are the major determinants of health status.[33] In particular, the Premier's Council found a strong relationship between socioeconomic status and health status. The Council claims that the health status of a population improves when socioeconomic disparities are narrowed.

Quebec's Commission d'enquête sur les services de santé et les services sociaux concluded similarly:

> Over the last 20 years, we have made considerable progress in developing knowledge in this area: the influence of risk factors and the synergistic effects which may exist between them are all the more clearly defined. In the light of such knowledge prevention takes on new strategic importance: it is now possible to influence directly certain determinants which are a condition to the appearance of health problems.[34] (Translation)

An often cited example is the French government's program to reduce infant mortality.[35] In the 1970s, French infant mortality rates were declining. (The same was true in North America.) Improvements in social and economic conditions were the main reason for the decline initially. However, during the 1960s and, especially, the 1970s, the main reason for

the decline was advances in the treatment of premature infants, rather than lower rates of prematurity, resulting in healthier newborns. The French government, therefore, decided to focus on reducing the rate of prematurity through broad social and economic policies.

Women were paid to attend prenatal care and were given food supplements. Maternal leave before delivery was increased to nine weeks. Pregnant women working in Paris were given a half-hour off at the beginning and end of the business day to enable them to avoid the most hectic part of rush hour. As a result, the French have reduced their rate of prematurity by 30 percent and their rate of very low birthweight (less than 1 500 grams) by 50 percent.

France's infant mortality rate has remained, like Canada's, nearly the lowest in the world. The major reason for Canada's decreased infant mortality rate, however, remains better treatment of premature, low birthweight infants, not the prevention of prematurity and low birthweight. France, therefore, has fewer children with disabilities related to prematurity. Even though modern neo-natal intensive care can save the lives of very tiny babies, many are destined to live with disabilities (e.g., mental retardation and chronic lung disease) associated with prematurity.[36] This is particularly true for infants weighing less than 1 500 grams at birth.

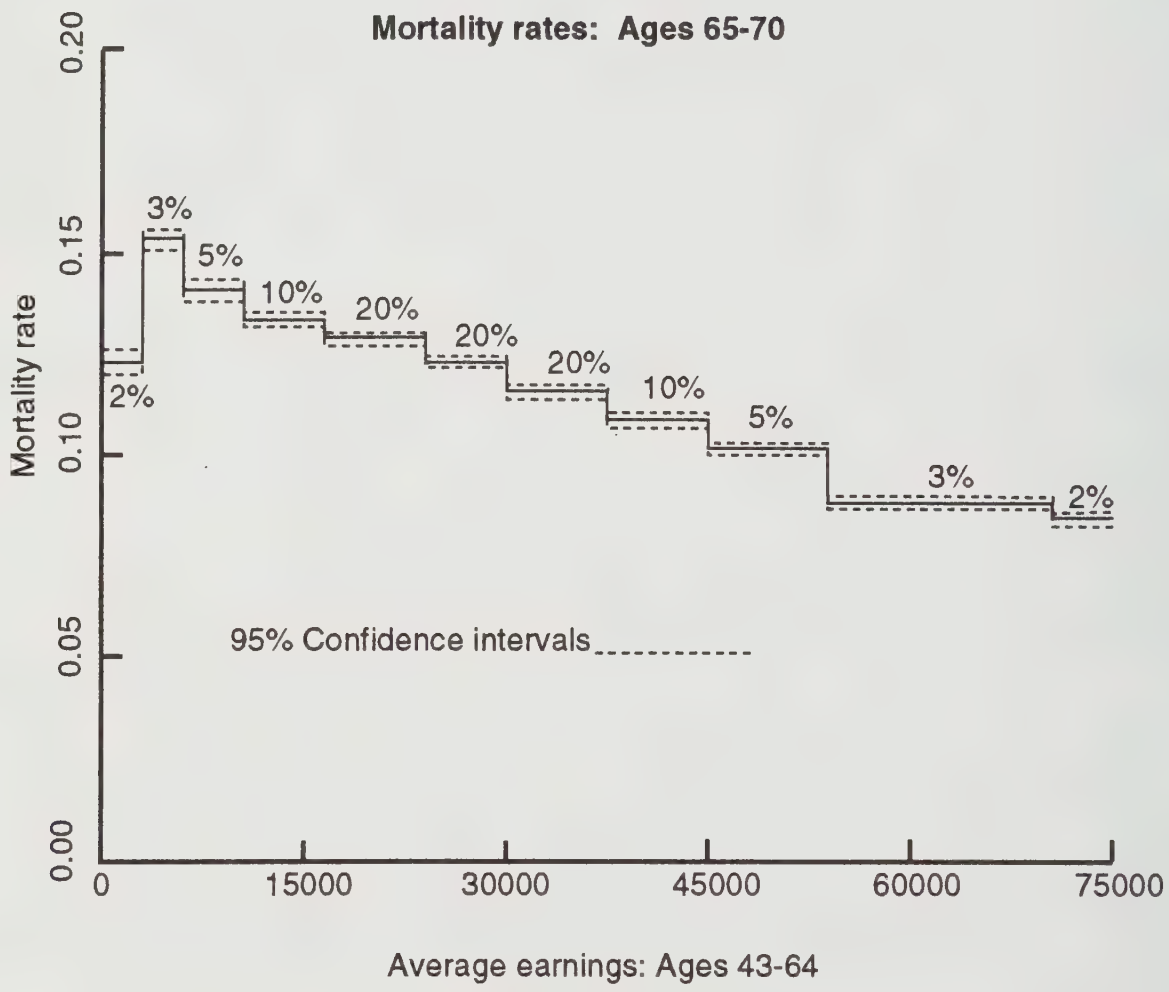
This example is drawn from a considerable body of evidence on the promotion of health. Some programs may take time to produce social and economic returns, but others, like maternal health promotion, can achieve major benefits within nine months or less.

It is also important to note that the health care system has relatively little ability to compensate for deficiencies in the other determinants of health. An English study conducted in the late 1960s and early 1970s illustrates this phenomenon.[37] More than 17 000 male civil servants working in London were examined between 1967 and 1969 and then observed over time for the development of heart disease and deaths recorded. The civil servants were divided into four classes. The administrative class was composed of senior administrators. The executive/professional class was composed of mid-level managers and professionals such as engineers. The clerical class was composed of clerks and other white-collar workers. The "other" class was composed mainly of manual labourers. Four percent of the research subjects in the administrative class died within the 10-year follow-up period, but 8 percent of the executive/professional class, 12 percent of the clerical class, and 16 percent of the manual labourers died during the same period. These differences are not trivial and occurred despite universal access to a national health care system.

A number of Canadian studies have also concluded that the health care system is limited in its ability to compensate for illness created by society's structural inequalities. The Canadian health care system is very well funded by international standards. But even the Canadian health care system has limited abilities to narrow the socioeconomic disparities in

health status.[38] One of the most comprehensive studies of socioeconomic differences in health status was completed recently by Michael Wolfson and colleagues at Statistics Canada. Dr. Wolfson's group used Canada Pension Plan data to determine the effect of average earnings before retirement on death rates. Figure 1 shows the overall results of the study. There is a strong relationship between average earnings in the 30 years before retirement and death rates after retirement. The men in the highest earning groups had only half the risk of dying between 65 and 70 years of age compared to the men with the lowest average earnings.

Figure 1. Male Mortality Rates and Average Pre-retirement Earnings



Source: M.C. Wolfson *et al.*, *Career Earnings and Death: A Longitudinal Analysis of Older Canadian Men* (Toronto: Canadian Institute for Advanced Research, 1991).

Establishing Strategies for Health

The first Canadian report to recommend goals or strategies for health was a 1974 document from Health and Welfare Canada known as the Lalonde Report.[39] One of its major recommendations was a goal-setting strategy. There was little follow-up to the Lalonde Report in Canada, but the document had a major impact on the development of health policy in the United States and Europe. The United States began to develop national health goals in 1979 and 1980.

The European Region of the WHO approved a set of health goals in 1984, taking a broader approach to health than had the Americans. The European goals emphasized the need to act on social and economic factors (especially structural societal inequalities), which were seen as major determinants of health. The first Canadian health goals were also proposed in 1984. In that year, Quebec's Conseil des affaires sociales (an advisory body to the minister of social affairs) proposed a series of goals. However, the province never adopted these goals.

In 1986, the Canadian Public Health Association, the WHO, and Health and Welfare Canada sponsored an international conference on health promotion. The conference adopted the Ottawa Charter for Health Promotion, which outlined five broad strategies for health:

1. build healthy public policy;
2. create supportive environments;
3. strengthen community action;
4. develop personal skills; and
5. reorient health services.

This document was preceded by another landmark Canadian report, *Achieving Health for All: A Framework for Health Promotion*, which was released by the Minister of National Health and Welfare in June 1986. This report identified three national health challenges, three health promotion mechanisms, and three implementation strategies. The "Framework for Health Promotion" summarized the changed philosophy of health policy as follows:

> As we broaden and deepen our understanding of health, we begin to perceive with greater clarity the importance and magnitude of the challenges now looming in the field of health. We also draw the conclusion that our system of health care as it presently exists does not deal adequately with the major health concerns of our time.

The Framework also concluded that the first step was to find ways of reducing inequalities in health status resulting from economic status:

> As we search for health policies which can take this country confidently into the future, it is obvious that the reduction of health inequities between high- and low-income groups is one of our leading challenges.[40]

The Ontario government established a Premier's Council on Health Strategy in 1987. The Council established five broad health goals in 1989:

1. shift the emphasis to health promotion and disease prevention;
2. foster strong and supportive families and communities;
3. ensure a safe, high-quality physical environment;
4. increase the number of years of good health for the citizens of Ontario by reducing illness, disability, and premature death; and
5. provide accessible, affordable, appropriate health services for all.

The Council saw these goals as establishing a framework for priorities and policy reform. Since 1989, the Council has elaborated objectives and targets for goals 2, 3, and 4.

Since 1989, Quebec and New Brunswick have also proposed health goals.[41] New Brunswick and Nova Scotia have established provincial councils of health with responsibility for coordinating an overall strategy for health.

Strategies for Reproductive Health

The fourth Ontario health goal is to "increase the number of years of good health for the citizens of Ontario by reducing illness, disability, and premature death." Objective 4.8 under goal 4 is to "reduce perinatal and infant mortality and long-term morbidity of perinatal origin."[42] The preamble to the objective refers to encouraging more research into mechanisms to prevent low birthweight. The five targets under this objective refer to reducing the rate of low birthweight (birthweight less than 2 500 grams), better surveillance for perinatal morbidity and congenital anomalies, and better availability of supports for parents.

The Quebec ministry of health and social services released draft health objectives in 1989.[43] Its fifth objective was to reduce the perinatal mortality rate to 6 per 1 000 live births by the year 2000. The strategy outlined to meet this objective focussed on preventing low birthweight and premature deliveries largely through social interventions (e.g., prenatal food supplements and outreach to ensure attendance at prenatal visits) with underprivileged women. Objective eight was to stabilize the spread of sexually transmitted diseases by the year 2000. The strategy to achieve this objective included sexuality education in schools, better accessibility to diagnostic and treatment services, and better contact tracing.

Governments are thus moving to elaborate broad strategies for health. Increasingly, medical and hospital care are being seen as tactics within this broad strategy. Many individuals and organizations have been calling for this shift since the Lalonde Report of 1974. This change in conceptual models of health and illness has been described recently by Professors Bob Evans and Greg Stoddart.[44]

Implications for New Reproductive Technologies (NRT)

Governments are now attempting to refocus their expenditures on the *determinants* of health as opposed to simply treating illness. If there is an accompanying flow of funds, there will be fewer resources available for high-technology services with high resource use for given outcomes. If this trend does develop, governments would be likely to focus expenditures and policies for reproductive health on social and economic interventions to prevent sexually transmitted diseases, low birthweight, and the delivery of premature infants. Within the health care envelope more resources would go to primary care rather than specialist or hospital care. In addition, new diagnostic tests and therapies for reproductive health care would be evaluated rigorously for their effectiveness and resource use.

There is no rigorous assessment of cost and effectiveness currently underpinning the allocation of resources for health care. Despite calls for a refocus of the health care system toward community health and health promotion, the overall allocation of resources within health care changed relatively little in Canada between 1975 and 1987 (see Table 2). Rosemary Proctor, a deputy minister with the Ontario Ministry of Community and Social Services, has recently written about this public policy dilemma. Proctor comments: "Where the new paradigm is weak is in its ability to suggest methods of intervention in the complex determinants of health to effect change or improvement."[45]

In fact, there is considerable evidence to support interventions on the broader determinants of health. In the 1970s a *conservative* French government thought the evidence in favour of social and economic interventions to reduce low birthweight and prematurity was strong enough to institute broad policies in these areas. In the 1990s even social democratic governments in Canada are waiting for more compelling reasons to act on the determinants of health. Clearly there are significant cultural as well as political barriers to adopting new ways of thinking about health and illness.

In some provinces, public health, family planning, and sexually transmitted disease clinics are available. Some jurisdictions have developed sexuality education programs, but these are uneven across the country. Public health and sexuality education programs must be funded directly by government (as opposed to through the practices of private physicians). Governments have generally been unwilling to provide new funding for any health programs if there is no visible, pressing public demand. There is little political or public pressure to act on concerns about health status as opposed to health care.[46] Governments almost never conduct formal health impact assessments of their policies, except environmental policies.

Table 2. Allocation of Health Care Resources in Canada, 1975 and 1987

Program area	1975 %	1987 %
Hospitals, other institutions, and capital expenditures	59.1	54.0
Medical doctors and dentists	20.6	21.5
Drugs	8.9	11.6
Public health	4.2	4.4
Home care	0.3	0.8
Other	6.9	7.7

Source: Canada Health and Welfare Canada, *National Health Expenditures in Canada 1975-1987* (Ottawa: Minister of Supply and Services Canada, 1990).

Almost all interveners at the Royal Commission's public hearings supported more programs to prevent infertility. However, this support has not generated public demand for infertility prevention. On the other hand, fertility treatment (especially IVF) has been particularly visible. When a provincial minister of health considers the funding of better programs to treat infertility, there is visible pressure for these services. There is little pressure for better programs to prevent infertility.

Inefficiencies Within the Health Care System

Ken Fyke, executive director of the Greater Victoria Hospital Society, differentiates between "doing the right things" and "doing things right."[47] The determinants of health and the development of strategies for health relate to doing the right things. For example, should Canadians put resources into preventing infertility, treating infertility, or treating colds?[48] Some of the issues and trends in current health care policy debates concern doing the right things, but more have to do with doing things right. For example, what is the safest, most cost-effective method of performing, CVS or what is the optimal number of prenatal ultrasound examinations?

The federal and provincial reports referred to earlier all noted that if the health care system were doing the right things *and* doing things right, great savings could be achieved. For example, Dr. Robert Brook, a leading health services researcher, claims that in the U.S. fee-for-service system, 40 percent of hospitalizations are inappropriate and 20 percent to 40 percent of surgical operations are unnecessary or dangerous.[49]

These problems result from the absence of fundamental mechanisms to assure quality of care and from the presence of a financing system that often provides perverse incentives and an organizational structure that breeds inefficiency. This section first outlines the evidence that there is

considerable inappropriate care delivered by Canada's health care system. Next, quality assurance in health care (including technology assessment) is discussed. Then the issues and trends in the financing and organization of health care are discussed. The implications for reproductive health care are detailed in each section.

The Problem of Inappropriate Care

Although it may be relatively simple in retrospect to determine that a particular diagnostic test or therapy has not helped an individual patient, *an inappropriate service should be defined as one which the best scientific evidence would indicate in advance would be of no net benefit to the patient* ***or*** *one which could be predicted to be of benefit but of no more benefit than one which is less expensive.*

Using this definition, there is substantial evidence of the provision of inappropriate services:

- there are dramatic differences in the rates of delivery of certain services between geographical areas, despite the similar health status of their populations;
- a large proportion of services are labelled as inappropriate when expert panels are convened to define standards of care for particular illness episodes;
- if consumers are allowed to make informed choices about their care, they often choose different services than if the options for care are presented in a traditional fashion; and
- different methods of paying doctors change the volume and mix of services (with no effect on health status).

Each of these points will be discussed in turn.

There are dramatic differences in the rates of delivery of certain services between geographical areas, despite the similar health status of their populations. Over the past 20 years researchers around the world have noted dramatic differences in the rates of provision of various services between countries, provinces, or states, and even smaller areas like counties.[50] For example, the rates of tonsillectomy in Canada vary from 100 per 100 000 in Quebec to over 300 per 100 000 in Saskatchewan.[51]

There are methodological problems associated with this type of research,[52] but certainly dramatically different expenditures without obvious differences in health status raise questions about the appropriateness of care. Either too much care is being provided in high-rate areas or too little in low-rate areas. Some authors have suggested that uncertainty in clinical decision making and the supply of health care resources lead to these regional variations.[53]

A large proportion of services are labelled as inappropriate when expert panels are convened to define standards of care for particular illness episodes. A great deal of medical practice is unevaluated. In many clinical situations there is no good evidence to guide practice. Even for problems

where there is fairly good experimental evidence, doctors are faced with individual patients for whom treatments must be *individualized.* Although some medical specialty societies, medical associations, and licensing bodies have issued guidelines for certain patient situations, for many clinical situations there are no agreed upon standards for care.

Several studies have recently evaluated the appropriateness of the delivery of various services using guidelines on practice developed by consensus panels of physicians and researchers. The largest exercise of this type was conducted in 1986 by the Rand Corporation of Santa Monica, California.[54] The Rand investigators found that 17 percent of coronary angiography and upper gastrointestinal tract endoscopy, as well as 32 percent of the cases of carotid endarterectomy, were clearly inappropriate.[55] Canada generally has lower rates of medical procedures and operations than the United States, but it does not appear that lower-rate areas necessarily have higher proportions of procedures that are appropriate. The Rand Corporation studied rates of procedures in 13 different sites across the United States. The rate of coronary angiography was 2.3 times higher in the highest-rate area compared to the site with the lowest rate. However, the *appropriate* proportion was 72 percent in the high-rate area and 81 percent in the low-rate site.

Other authors have reported similar findings.[56] A York University survey of Canadian physicians in 1984 showed that the doctors believed that 15 percent of the days of patient care in their local hospital were unnecessary.[57] A recent paper delivered to the Canadian Paediatrics Society suggested that 24 percent of paediatric hospital admissions were inappropriate.[58]

If consumers are allowed to make informed choices about their care, they often choose different services than if the options for care are presented in a traditional fashion. It is increasingly appreciated that a patient's own values and preferences might be the key factors in determining appropriateness for many services. This is particularly true for elective procedures, but it has also been found for some curative procedures.[59] Recently researchers have used interactive video disc technology to allow patients to become informed about elective prostate surgery. When patients have an opportunity to tailor their counselling using the interactive technology, they are half as likely to request surgery as patients who simply discuss the procedure with a surgeon.[60] Other research has indicated that physicians are poor communicators, misreading patient preferences and frequently misunderstanding what their patients have really said.[61]

Different methods of paying doctors change the volume and mix of services (with no effect on health status). It has been noted for some time that different rates of servicing are associated with different methods of remuneration of physicians.[62] The most comprehensive study in this area was the Rand Health Insurance Experiment. In one part of the study, more than 1 600 patients were randomly allocated to receive their health care from either the Group Health Cooperative of Puget Sound (a Seattle-based,

non-fee-for-service health maintenance organization [HMO]) or fee-for-service providers in the Seattle area. Because the patients were allocated at random, there were no differences between the patient groups on measurable characteristics; nor were there likely to be any significant differences on unmeasurable characteristics that could affect health status.

At the end of the experiment there were no significant differences in the health of the two groups of patients, but there was a very large difference in costs. The average costs of the patients enrolled in the HMO were 25 percent less than those seeing fee-for-service doctors; the difference was attributable almost entirely to 40 percent fewer hospital days.[63]

Some caveats must be added to the results of the Rand Health Insurance Experiment, but they don't change its overall results.[64] Several Canadian studies, although less rigorous than the Rand Health Insurance Experiment, also indicate that fee-for-service practice increases costs of care.[65]

The influence of method of payment for physician services helps explain one of the barriers to the prevention of chlamydial infection, a major cause of infertility. Private, self-employed doctors reimbursed by fee-for-service payment are responsible for most of the health care of women of reproductive age in Canada. Typically, gynecological examinations (which are necessary for testing for chlamydia) pay extremely poorly per unit of time required. There is typically little or no payment for counselling about treatment for chlamydia or its prevention. Most doctors have had little formal training in counselling regarding individual behaviour change.

Several recent Canadian documents and reports have expressed concern about the appropriateness of care delivered through the system:

- the New Brunswick Commission on Selected Health Care Programs noted, "There is no doubt that much more could be spent on the health care system, but it is equally true that better value, in terms of health status protection or improvement, could be obtained for funds currently allocated to health care;"[66]
- the Nova Scotia Royal Commission on Health Care said, "... the Royal Commission contends that the capital and human resources allocated to health care can be more efficiently utilized so as to realize better value for the money spent. Research suggests that current patterns of health care delivery and utilization in Canada are frequently ineffective and inefficient;"[67] and
- the Ontario Health Review Panel (Evans Report) said, "Evidence of inappropriate care can be found throughout the Province's health care system, from inappropriate institutional admissions to overuse of medications among the elderly."[68]

All the evidence points to the conclusion that there is at least some inappropriate health care delivered to Canadians. This is not necessarily

the fault of individual providers. Rather, it is related to the structure and financing of medicare. Fee-for-service medical practice and the lack of quality assurance have led to many of the inefficiencies seen. The next section discusses the issue of quality assurance in health care.

Quality Assurance and Technology Assessment

There are several definitions for quality assurance; the term is sometimes used synonymously with utilization management or utilization review. Professor Jonathan Lomas of McMaster University has proposed the following definition of quality assurance:

> The measurement of health care activity, and the outcomes of that activity, in order to identify whether the expected objectives of the activity are being achieved and, when this is not the case, to respond with effective action to reduce the deviations from objectives.[69]

Dr. Geoffrey Anderson of the University of British Columbia and Professor Lomas have outlined a model for quality assurance.[70] Figure 2 shows a modified version of this model.

Establishing Standards and Technology Assessment

The first component in the model is the establishment of standards for procedures and services. This process should, ideally, use the best possible scientific evidence on efficacy and effectiveness.[71] The standards should be written and sufficiently explicit that their attainment may be easily and clearly determined. As much as possible, the standards should pertain to patient outcomes, not just structure or process.

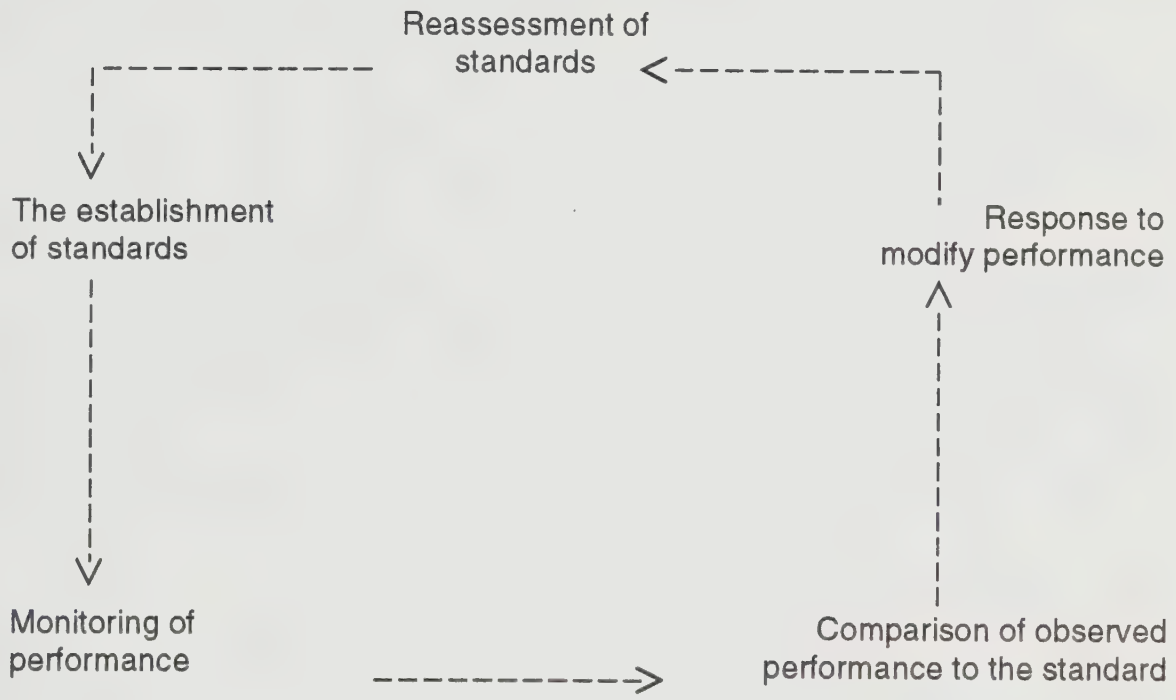
Patient preferences can determine the appropriate choice for many diagnostic tests and therapeutic procedures. Innovative techniques have recently been developed for eliciting patient preferences, including interactive video discs. Infertility is not a life-threatening condition; informed choices by patients should therefore guide decision making.

The assessment of technology and other health care interventions in Canada is inadequate and uneven.[72] The federal government is reassessing its process for the review of medical devices. However, it is much easier to market a new device than a new drug. At present, review and approval are required only for the following devices:

- contact lenses designed or represented for prolonged wear
- menstrual tampons; and
- any device designed to be implanted into the tissues or body cavities of a person for 30 days or more.

Drug manufacturers must prove their products' efficacy for certain clinical indications before they are approved in Canada. However, once a drug is approved for one indication it may be prescribed for others fairly easily.[73] Medical devices must be proved safe, but there are not necessarily requirements that they be proved efficacious.

Figure 2. Model of Quality Assurance in Health Care



The Conference of Deputy Ministers of Health established the Canadian Coordinating Office for Health Technology Assessment (CCOHTA) in 1989. The CCOHTA has an annual budget of $500 000, including $250 000 for salaries and $250 000 for operating expenses. The Quebec Ministry of Health and Social Services established their technology assessment unit in 1988. The British Columbia government established the B.C. Office of Health Technology Assessment in 1990. Ontario has announced its intention to establish a technology assessment unit. All these organizations put together, however, are unable to conduct many actual evaluations.

Most countries and progressive corporations attempt to spend a minimum of 3 percent of gross expenditures on research and development to remain efficient and competitive. Canada spends only 0.4 percent of health care expenditures on any form of research.[74] Even so, the vast majority of these funds are spent on basic lab research or pharmaceutical trials, conducted primarily to license a pre-existing product for the Canadian market. A small proportion is spent on epidemiology, public health research, technology assessment, quality assurance, health services organization, or management operations research.

Most of the funding for epidemiology, health services, technology assessment, quality assurance, and public health research comes from the National Health Research Development Program (NHRDP). The federal government will cut back the funding of this program by 8 percent in the fiscal year 1991-92.[75] The budget of the NHRDP amounts to about one-twentieth of one percent (0.05 percent) of the total spent on health care in Canada.[76] The cutbacks to the NHRDP mean that few new research projects can be funded. These cutbacks are not nearly balanced by the increase in funding for the CCOHTA and the new technology assessment units in the provinces.

Monitoring Performance

The second component of the quality assurance model is the monitoring of performance. The quality assurance process should collect data that would allow evaluators to determine the extent to which standards have been attained. Because it is desirable for the standard to relate to actual patient outcomes, performance monitoring should include information on health outcomes, not just process or structure. The data collection process should not be so arduous, however, that it is never completed. There is currently little routine collection of data on clinical performance that would be useful for quality assurance activities.

Comparing Performance to Standards

The third component of the quality assurance process is the comparison of the provider's performance with the established standard. As well as assessing the provider's performance according to each standard, there should also be an overall evaluation of the provider's performance. There is almost none of this activity in Canada's health care system.

Responses to Modify Performance

The fourth component is the response of the organization to modify performance that fails to meet established standards. Eisenberg has outlined six mechanisms to improve health care practice:[77]

1. education;
2. feedback;
3. participation;
4. administrative rules;
5. financial incentives; and
6. financial penalties.

Some researchers have found that education and feedback can improve the quality of care.[78] However, education and feedback alone are usually not very effective.[79] In general, the other four strategies are more effective than education and feedback alone. Also, combinations of strategies are usually more effective than any one strategy alone.

In 1986, the SOGC established guidelines for Caesarian sections.[80] However, simply releasing the guidelines was not sufficient to change clinical practice.[81] Researchers from McMaster University have found that the use of the local medical leadership to promulgate the guidelines did result in a change in clinical practice and a reduction in the rate of inappropriate Caesarian sections.[82] There are other examples in the medical literature of how the implementation of quality assurance activities has improved the appropriateness of servicing.[83]

Reassessing the Clinical Standard

After a quality assurance cycle is completed there should be a reassessment of the standard. New research would render some previously accepted clinical standards obsolete.

Total Quality Management

Dr. Donald Berwick, the former Vice-President for Quality Assurance for the Harvard Community Health Plan (a Boston-based health maintenance organization with over 800 000 members), has suggested that traditional North American industrial quality assurance programs rely too much on "sticks" and not enough on "carrots."[84] Berwick suggests that health care organizations focus instead on creating environments that enhance their employees' productivity. This process is sometimes called "total quality management" or "continuous quality improvement." Berwick claims that an organization that is designed specifically to generate continual improvements in the quality of its "products" will produce goods and services of higher quality than an organization that simply weeds out the bad apples after the fact. The aim should be to prevent the apples from going bad in the first place.

The Use of Quality Assurance in the Canadian Health Care System

There is very little quality assurance in the Canadian health care system. The guide for hospital utilization review, published jointly by the Ontario Hospital Association, the Ontario Medical Association, the Ontario Ministry of Health, and the Hospital Medical Records Institute, based its guidelines in part on the following premise:

> *Every hospital can improve its utilization experience* and therefore should implement a utilization management program. Although the type and significance of utilization problems vary greatly among hospitals, *major improvements in the effective utilization of hospital resources in Ontario can be accomplished* through the development of strong utilization management programs. (Emphasis in original)[85]

The New Brunswick Commission on Health Care noted,

> In New Brunswick there is insufficient attention being given to utilization management. Hospital boards are quite passive on the question and most hospitals do not have an individual assigned to coordinate utilization management activities.[86]

A recent Canadian survey of provincial licensing bodies for physicians, nurses, dentists, pharmacists, and optometrists found that these professions were unlikely to have comprehensive quality assurance programs in ambulatory care.[87] In particular, only four of 50 organizations had any explicit standards that related to patient outcomes. Only six had explicit prospective criteria for assessing a practitioner's performance. Only three had formal review processes for reassessment of standards. Of more than 350 000 licensed health professionals, only 0.04 percent (approximately 1 in 2 500) had their licences suspended because of concerns about quality during a three-year period.

There are many structural barriers to implementing quality assurance programs in Canada. They include the following:

- there are few goals for health or health care. As a result, there are few criteria for the funding or evaluation of programs;
- there are few standards or guidelines for medical practice. Sometimes there are several different standards promulgated by different organizations;
- responsibility for quality assurance is unclear. In some provinces, the legislation establishing a licensing organization for physicians appears to give responsibility for establishing and maintaining standards of medical practice to these organizations. However, in other provinces the licensing body is not given this authority, and it is not even mentioned as one of the objectives of the organization;
- much of medical practice is unevaluated, so that standards must often be developed without a proper evidentiary base;
- there is little routine monitoring of the practice of health professionals;
- there are few effective tools available to modify the performance of practitioners; and
- there are few clinical managers, especially physician-managers. As a result, quality assurance programs often depend upon the unpaid labour of physicians.

Trends in Quality Assurance

Recently there has been a proliferation of clinics providing services normally provided in hospitals. *In vitro* fertilization is one of the procedures provided in such clinics. In response to these developments, the province of Ontario passed the Independent Health Facilities Act in 1989. The act prohibits the private billing of patients for procedures covered by OHIP and requires the development of quality assurance programs. The College of Physicians and Surgeons of Ontario is responsible for the development of standards and quality assurance programs for clinics covered by the Independent Health Facilities Act. The government of Ontario decided in

the spring of 1991 not to include IVF clinics under the act. The College of Physicians and Surgeons of Ontario had developed draft standards for these clinics, but these cannot be used unless IVF clinics are brought within the ambit of the act.

Governments have been slow to act in the area of quality assurance. Provincial governments are very concerned about being accused of interfering with the doctor-patient relationship. Professional consensus and research findings have indicated that quality of care can be enhanced through:

1. the establishment of standards using scientific methods of literature review under the auspices of the professional organization(s) that has (have) the most credibility with the relevant specialty group;
2. the use of local medical leadership (educational influentials) to communicate with community practitioners;
3. the repeated feedback of individual practitioners' clinical performance compared to peers in a style that is understandable and non-threatening; and
4. a focus on improving the average performance of the group rather than simply identifying poor performers.

There are signs that the medical profession is interested in quality assurance. More provincial licensing organizations are moving to random audit of doctors' office practices. The College of Physicians and Surgeons of Ontario has gained considerable experience through its standard-setting[88] exercises for the Independent Health Facilities Act. The SOGC has been part of important research on improving the appropriateness of the use of Caesarian sections. The past president of the SOGC, Dr. David Popkin of Saskatoon, has urged the Society to establish practice guidelines because "Society has entrusted physicians with providing services which are up-to-date, safe and in the best interests of the patient"[89] and because "It is time to get on the bus or be hit by the bus."[90]

Implications for New Reproductive Technologies

There have been a number of concerns raised about quality assurance and NRTs. For example, it does not appear that counselling of infertile couples is being conducted in a uniform fashion. There are no effective standards for counselling and there is no monitoring to ensure that it is conducted in a non-biased fashion. According to the report on the Royal Commission's public hearings, Dr. Christo Zouves said that 35 percent of his patients chose not to have IVF after the initial counselling session, while Dr. Patricia Gervaize said that less than 1 percent of her patients chose not to proceed after the initial counselling. There are no standards for success for IVF clinics and no requirement for proprietors of private IVF clinics to disclose their success rates. Some Canadian IVF clinics are as

successful as any in the world, whereas at least one has a very low success rate.

The federal and provincial reports on health care in the past decade have all asserted that it is very important to assess new and existing technologies and the processes of health care delivery to develop an efficient and effective health care system. Governments find themselves short of funds for new programs, however, and evaluative programs must compete with operational programs for new money. It is obvious that there is very little political demand for evaluation. There are no angry demonstrations for more funds to *evaluate* a new piece of equipment or health service. There may well be demonstrations for the *operational and capital funding* of these programs *without* evaluation. It is not likely that the current political environment will allow significant funding for evaluation, technology assessment, and quality assurance.

If the Royal Commission believes there should be more evaluation of certain technologies, it will have to make this recommendation very strongly and frame it in light of the need to attract public and political support if such recommendations are to succeed in changing public policy.

However, there are some positive developments in quality assurance. First, some within the medical profession are keen to move but are looking for leadership from government. Government needs to provide assistance with data collection and analysis. Government must also put more resources into technology assessment and program evaluation. Current efforts are the equivalent of attacking a forest fire with a water pistol. Government also needs to represent the public by being clearer about the scientific processes required to establish standards and the desired ultimate outcomes of care. If government can provide leadership, there could be rapid developments in quality assurance over the next decade.

Trends in the Financing and Organization of Health Care

There are more and more concerns that the traditional fee-for-service doctor is practising in an environment that obstructs quality and increases the costs of care. Although the evidence to support this position has been available for at least a decade, provincial governments are just now showing a willingness to act. This section outlines the developments in alternative methods of physician payment, new models for the delivery of primary (first-contact) care, and changes in the organization of specialty and hospital care.

Alternative Methods of Paying for Physicians' Services

Several studies have shown that paying doctors on a fee-for-service basis increases the overall cost of care without improving the outcomes of care. The provincial and territorial deputy ministers of health announced a national strategy at their conference in Banff in January 1992. One of the policy directions they announced was

> Fee-for-service should be replaced wherever that method of payment aligns poorly with the nature or objective of the service being provided.[91]

Most of Canada's physicians are paid on a fee-for-service basis, but there are some alternative payment plans for doctors in all provinces. Ontario is also developing a model called the comprehensive health organization (CHO). The CHO would be given a fixed sum (a capitation payment) for each regular patient on its roster. The CHO would provide all needed medical and acute hospital care from this funding. The CHO would be governed by a board made up of representatives from institutions, doctors, other health care providers, consumers, and municipalities. These CHOs would function essentially as regional health authorities. The CHOs now in the most advanced state of development are in rural and remote areas of Ontario.

Ontario and other provinces are also developing new models of primary (first-contact) care to be reimbursed on a non-fee-for-service basis. These are discussed in the next section.

New Models of Primary Care

The Royal Commission heard various criticisms of the provision of health care services. This report has outlined some other problems with the quality of care provided by the health care system.

Doctors often don't communicate effectively with patients. This can result in lack of attention to patients' real concerns, poor compliance with prescribed therapies, and the administration of diagnostic tests and treatments that patients would not choose themselves if they had the opportunity to make an informed choice. There are also complaints about the way doctors (who are mainly male) deal with women's health problems. A recent letter to *The Medical Post* (from a male doctor) provides an example:

> Women have problems with breast feeding because the staff who are supposed to help them breast feed do not and cannot help them, since they have never been trained to help women with breast feeding.[92]

Furthermore, governments are concerned about the rising cost of ambulatory physicians' services, which has been related, in part, to the fee-for-service method of payment. Nurses and other health professionals are concerned that they have little opportunity to provide primary care. As a result of these phenomena, some provinces have been exploring new models of primary care.

Quebec began to develop its community health clinics in 1972 as part of the reform of its health and social services system. The centres are called CLSCs (centres locaux de services communautaires). There are now over 160 such centres in the province, and it is estimated they provide primary health care to about 5 percent of the population.[93]

Ontario has 41 community health centres and another 30 in the planning stage. Saskatchewan and Manitoba have about half a dozen each,

and the other provinces have small numbers. There is no uniform definition of the terms "community health centre" or "community clinic." However, community health centres usually pay doctors on other than a fee-for-service basis, have non-physicians on staff, and have some consumer or community participation in governance.

In Ontario there are about 90 health service organizations (HSO) funded by capitation — a fixed payment for every regular patient on the HSO's roster. The capitation payment is only for ambulatory care, but there are bonuses if the HSO's hospitalization rate is less than the provincial average. The government is concerned that this program is not performing as it should;[94] and it has terminated the HSO contracts and is negotiating new agreements.[95]

Community health clinics have been found to be less expensive than fee-for-service practice in Ontario and Saskatchewan.[96] There were no signs that the savings occurred because the CHCs provide inferior care. Studies in Quebec have shown that CLSCs provide care of higher quality for patients with headaches,[97] more appropriate cancer screening,[98] better cancer prevention services,[99] and more complete childhood immunization.[100]

Pineault surveyed a sample of 616 Quebec general practitioners in different practice settings.[101] He found that CLSC doctors were younger and were more likely to practise in a group, do less emergency room and hospital work, and perform more community health activities. The CLSC doctors also were more positive about working in multi-disciplinary teams, were interested in the demedicalization of health care, favoured patient involvement in their care, and were less likely to endorse a strict biomedical model of health care. Pineault suggests self-selection is most likely responsible for the different attitudes displayed by physicians practising in different settings.

During the 1970s hundreds of feminist health centres were established in the United States, but there are very few in Canada. A notable example is the Women's Health Clinic in Winnipeg. Most articles written about women's health clinics have been descriptive rather than evaluative.[102] A thorough literature search conducted for this report found no articles comparing outcomes at women's clinics with those of services from more traditional providers. The literature on non-fee-for-service practices and patient preferences would indicate, however, that this model might be more effective and efficient than traditional medical practice.

Rationalization of Specialty and Hospital Care

Canada's health care system developed in an era without much technology. One hundred years ago, very few services had to be provided by specialized personnel in specialized facilities; most surgery was performed by general practitioners in people's homes. Now, even routine surgery is referred to specialists and is almost always performed in hospitals.

There are often economies of scale associated with the use of high-technology services. It is more efficient to have one hospital maximize the use of its CAT scanner by sharing it with another hospital than to provide two hospitals with a CAT scanner each that is used part-time. Gradually, provincial governments have moved to rationalize the distribution of high-technology equipment and specialized personnel.

Provincial governments are also investigating vertical integration of services. This term refers to the financial linkage of different levels (hence "vertical" integration) within the health care system. This section discusses the issues and trends for vertical integration and regionalization of health care services.

Vertical Integration of Health Care Services

Vertical integration of health budgets means linking the budgets for different *levels* of health care (e.g., institutional and ambulatory care). The advantage of this financing model is that resources can easily be transferred from one service to another according to patient need. Otherwise, it may take years to reallocate money from an institutional program to one in the community.

Vertical integration can be accomplished in different ways. The Quebec Ministry of Health and Social Services has been decentralizing its operations to the regions for 20 years. Gradually the regional councils are gaining power over budgets. The latest reforms have outlined a process for democratic election of some members of these councils. There are still limits to the authority of the regional councils, but eventually they will have considerable power to reallocate resources within their envelopes.

The Ontario Ministry of Health is investigating two different mechanisms for vertical integration. One is through devolution of at least some budgetary power to a local authority,[103] which might be similar in structure to a local school board. Or Ontario might build on the existing District Health Councils, which are appointed voluntary planning boards. The other model of vertical integration is the comprehensive health organization or CHO described in the previous section.

Regionalization of Health Care Services

The province of Quebec has already decentralized much of the authority over the health care system to regional councils. Most other provinces have recently investigated, or are now investigating, models of regionalization. Sometimes regionalization is an attempt to devolve control over services to a more appropriate level. Sometimes regionalization is seen as a method of vertically integrating budgets to allow rationalization of services. However, sometimes regionalization can lead to less democracy and more bureaucracy if services are devolved to undemocratic local structures. It is important to clarify the purposes of regionalization:

1. Which services are being regionalized?
2. Is there greater or less consumer/community control?

3. Are services being rationalized? Are there economies likely to be achieved because of the elimination of duplicated services?
4. Will services be better coordinated?

There is considerable evidence that some (but not all) medical procedures that require special skills are performed more successfully in specialized facilities by special personnel.[104] It therefore makes sense to centralize some medical care (e.g., neo-natal intensive care) in certain facilities. These procedures would be those characterized by the following:

- high capital cost;
- considerable skill and expert personnel requirements; and
- treatment of acute conditions.

Implications of Changes in Health Services Financing and Organization

Quebec has developed a new model of primary care (the CLSC) and made it the cornerstone of its system of health and social services. Ontario has developed 20 new community health centres in the past four years, but they are still at the margins of the health care system. No other province has developed significant numbers of new models of primary care. In the past these clinics have been opposed by the medical establishment.[105] Despite the recent pledge by provincial health ministers to move away from the fee-for-service mode of payment for physicians, it is not likely that provinces other than Ontario and Quebec will promote community health clinics in the foreseeable future. It is likely that they will attempt to move more doctors away from fee-for-service but allow them to remain as private entrepreneurs.

If the Royal Commission wishes to encourage new models of primary care, it will have to advocate the recommendation strongly.

These developments may have significant implications for NRTs. If there is a move to vertical integration, these services will be competing directly for funding with other reproductive services. If services are increasingly rationalized, then newer technologies (if available at all) will be confined to fewer facilities.

Consumerism and the Women's Movement

Increased consumer sophistication and the modern women's movement developed in the 1960s. These trends are now showing some impact on health care in the 1990s. There is considerable evidence that doctors have poor communication skills. This means that doctors don't necessarily ensure that patients comply with therapeutic regimens. Further, doctors frequently administer tests or therapies that patients would not agree to if they could have made an informed choice. Many women have been making these points about traditional reproductive health care for decades. However, this critique has become mainstream in the past 10 years.

It is therefore understandable that there was disagreement among interveners before the Royal Commission about whether NRTs facilitate or decrease choice for women. This disagreement was seen most sharply between women's and consumer groups. Consumer groups saw IVF and other NRTs as increasing women's reproductive choices. However, women's groups saw NRTs as increasing the medicalization of reproduction and therefore restricting women's choices. In truth, both might be right. If women were allowed to make genuinely informed choices about these technologies, less societal regulation would be required. However, if women (and other patients) are not really given the opportunity to make a decision that reflects their own values and preferences, then more state regulation may be warranted.

The analysis of the Royal Commission's public hearings questioned whether it is possible for women to make informed, free choices with regard to sex-selection or surrogacy[106] in a society marked by social inequality on the basis of sex, race, class, etc.

The reactions of women's groups to NRTs may reflect the long history of grievances about physicians' control of women's reproductive functions. Several historians have documented the simultaneous rise of physicians and the eradication of midwives and other (mainly female) traditional healers.[107] Many of the "witches" killed during the late Middle Ages were midwives and other female healers. Ehrenreich and English (1979) quote from an eighteenth-century petition to the English Parliament from physicians lamenting the "worthless and presumptuous women who usurped the profession." The doctors went on to call for fines and imprisonment for women who attempted to practise medicine.

Mitchinson has documented some of the abuses suffered by women treated by male physicians in nineteenth-century Canada.[108] For example, at the London (Ontario) asylum, during the 1890s, women were routinely anesthetized against their will for gynecological examinations and, not infrequently, mutilating surgery.

It may be easier to understand resentment on the part of women's groups toward medicine or suspicion of NRTs if we consider the history of obstetrics and gynaecology. Many reproductive interventions introduced by doctors have later been found to be ineffective or dangerous. For example, during the 1950s and 1960s many women were given diethylstilbesterol (DES) during pregnancy, despite there being no evidence of its benefit and some evidence that it was dangerous.[109] Suspicion is enhanced by drug company funding of continuing medical education and even the voluntary registry of IVF.

Other recent reproductive interventions proved ineffective or harmful include strict limits on weight gain during pregnancy, routine prepping during labour, routine episiotomy, labour without social support, and electronic fetal monitoring. In fact, electronic fetal monitoring is still used routinely in some hospitals despite several controlled trials showing that it is of no benefit in lower-risk labours but does increase the rate of Caesarian section. Midwifery and a "softer" approach to birthing (including social

support) have continued to come under attack by some physicians, even though scientific evidence has been accumulating that substantiates this overall approach.

The Royal Commission is the latest battleground for a conflict that is at least a thousand years old. The conflict is between traditional female healers (e.g., midwives) and their ideological supporters and (mainly) male allopathic doctors and their supporters.

The organized women's community has led demands for more consumer input into treatment decisions. It has also led the call for changes in the organization and governance of health services. These societal trends will continue as women attempt to develop their own agenda for health and health care. This trend is assisted by the following:

- concerns on the part of government and the medical profession about the lack of evaluation of medical therapies;
- concerns on the part of government about the cost of health care, particularly the cost of unevaluated high-technology medical care; and
- growth in political power of non-physicians in health care (nurses, other health care workers, administrators).

The Changing Federal-Provincial Relationships in Health Care

The federal government actively encouraged the provinces to develop their medicare programs. In fact, Ontario opposed the medical care insurance legislation of 1966[110] and Alberta and Ontario opposed the Canada Health Act of 1984. However, in more recent years the federal government has been withdrawing its money for health care and its leadership for health policy. It is forecast that within 10 to 15 years the federal government will no longer transfer any cash to the provinces for their health care programs.

The provinces are concerned about this unilateral decrease in funding, but recent court decisions have confirmed the authority of Parliament unilaterally to change the terms and conditions of its grants to the provinces.

This section reviews the separation of powers for health policy in Canada, the present enforcement of the Canada Health Act, and the implications for the Royal Commission.

Constitutional Authority

It is generally accepted that the provinces have the responsibility for health care. However, as stated by Mr. Justice Estey, health *policy* may be considered the responsibility of either the federal or provincial governments.

> Health is not a subject specifically dealt with in the *Constitution Act* either in 1867 or by way of subsequent amendment. It is by the Constitution not assigned either to the federal or provincial legislative authority. Legislation dealing with health matters has been found within

> the provincial power where the approach in the legislation is to an aspect of health, local in nature ... On the other hand, federal legislation in relation to "health" can be supported where the dimension of the problem is national rather than local in nature ..., or where the health concern arises in the context of a public wrong and the response is criminal prohibition ... In sum, "health" is not a matter which is subject to a specific constitutional assignment but instead is an amorphous topic which can be addressed by valid federal or provincial legislation, depending in the circumstances of each case on the nature or scope of the health problem in question.[111]

In other words, the Constitution does not necessarily preclude an assignment of responsibility for health policy as dictated by the times and issues. For example, economies of scale argue for the bulk of health research to be conducted at a national level. In a similar vein, only the federal government can conduct health surveys that would answer national questions.

The Canada Health Act and Canadian Health Policy

The Canada Health Act of 1984 provides directions for the further development of health policy. The preamble to the act says (in part):

> Whereas the Parliament of Canada recognizes: ...
>
> — that Canadians can achieve further improvements in their well-being through combining individual lifestyles that emphasize fitness, prevention of disease and health promotion with collective action against the social, environmental and occupational causes of disease, and that they desire a system of health services that will promote physical and mental health and protection against disease;
>
> — that future improvements in health will require the cooperative partnership of governments, health professionals, voluntary organizations and individual Canadians;
>
> — that continued access to quality health care without financial or other barriers will be critical to maintaining and improving the health and well-being of Canadians;
>
> And whereas the Parliament of Canada wishes to encourage the development of health services throughout Canada by assisting the provinces in meeting the costs thereof ...

Section 3 of the act says:

> It is hereby declared that the primary objective of Canadian health care policy is to protect, promote and restore the physical and mental well-being of residents of Canada and to facilitate reasonable access to health services without financial or other barriers.

Several key policy directions may be derived from the preamble and section 3 of the Canada Health Act:

1. health policy is much more than health care services;

2. the achievement of any health status objectives must be through a multi-sectoral approach;
3. health care services should be available without undue barriers;
4. the federal government should continue to provide funding to the provinces' health care systems; and
5. the purpose of health care services is to improve the health status of Canadians.

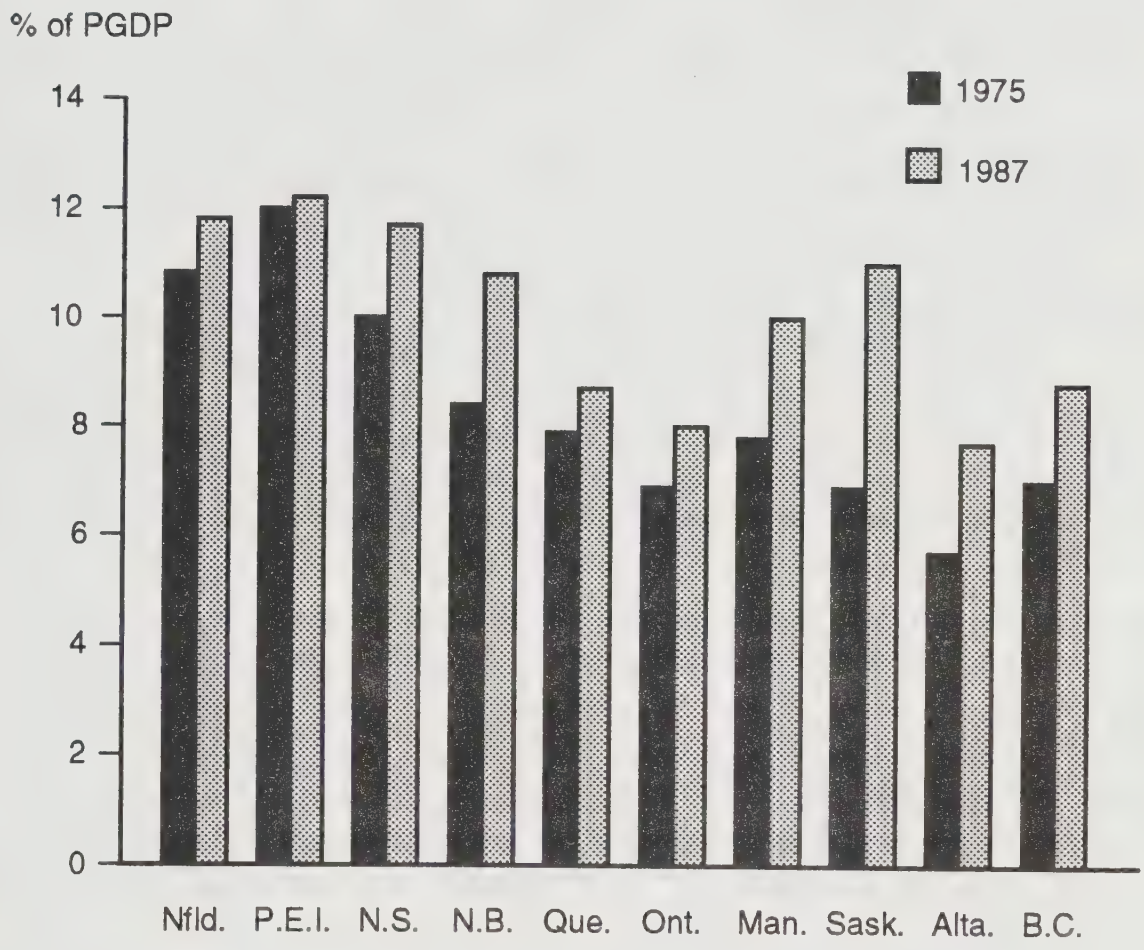
Various participants in the debate about health policy have pointed out that the Constitution Act of 1982 establishes equality of opportunity for well-being as an objective of the Canadian confederation:

> *Section* 36.
> (1) Without altering the legislative authority of Parliament or of the provincial legislatures, or the rights of any of them with respect to the exercise of their legislative authority, Parliament and the legislatures, together with the government of Canada and the provincial governments, are committed to
> (a) promoting equal opportunities for the well-being of Canadians;
> (b) furthering economic development to reduce disparity in opportunities; and
> (c) providing essential public services of reasonable quality to all Canadians.
> (2) Parliament and the government of Canada are committed to the principle of making equalization payments to ensure that provincial governments have sufficient revenues to provide reasonably comparable levels of public services at reasonably comparable levels of taxation.

Some might maintain that section 36 refers only to the formal program of equalization payments. Only section 36, subsection (2) refers to equalization payments, however. Section 36, subsection (1) does not refer to the equalization program and could well be interpreted as a series of global objectives to be achieved by the equalization program *and other federal programs as necessary.*[112] The EPF program is a *de facto* equalization program. If the cuts to EPF are not soon balanced by other transfers to the poorer provinces, the federal government will, by definition, be making it more difficult for the poorer provinces to deliver public services of reasonable quality.

One of the purposes of transfer payments is to equalize service delivery across the country. Without these funds the poorer provinces might lack the resources to provide the same level of service as the wealthier provinces. For example, in 1987, before the most recent recession, Newfoundland spent nearly 12 percent of its gross provincial product on health care, compared to 7.7 percent for Alberta and 8.2 percent for Ontario.[113] (See Figure 3 for a graph comparing the proportion of gross provincial products provinces spend on health care.) Thus federal financial cutbacks endanger Canadians' equality of access to health services.

Figure 3. Provincial Health Expenditures as Percentages of Provincial Gross Domestic Products (PGDP), 1975 and 1987



Source: Canada, Health and Welfare Canada, *National Health Expenditures in Canada 1975-87* (Ottawa: Minister of Supply and Services Canada, 1990).

A further consequence of federal cutbacks is the diminished capacity of Health and Welfare Canada to coordinate the national development of services for reproductive health. The family planning division was disbanded in 1985. There is now one position, in the community health branch, for a family planning consultant. The consultant is charged with the major role in implementing the recommendations of the recently completed report on adolescent health.[114] The consultant has not been able to develop an inventory of family planning clinics.

The sexually transmitted disease division has one MD position, two non-MD epidemiologist positions, and one secretarial position. The division is supposed to coordinate the development of a national strategy for the control of sexually transmitted diseases. Resources are so tight that the

division cannot even collate the contact-tracing procedures used across the country. There are no resources available to repeat the Youth and AIDS survey. Health and Welfare Canada recently let lapse the mandate of the Expert Interdisciplinary Advisory Committee on Sexually Transmitted Diseases (STDs) in Children and Youth (EIAC). There are no other advisory committees on STDs.

These cutbacks in resources and leadership by Health and Welfare Canada translate into a lack of a national strategy for reproductive health. These cuts, in concert with other cutbacks in Health and Welfare programs and diminished federal cash transfers, have left a national strategy for reproductive health in a vacuum.

Enforcement of the Canada Health Act

The Canada Health Act details five criteria that provincial health insurance plans must meet to be eligible for 100 percent of their estimated federal contribution. Not all the provinces are complying with these five criteria, but none is being penalized by the federal government. This section outlines the current problems with enforcement of the Canada Health Act.

Accessibility and Comprehensiveness

There are no clear answers to the question of what services provincial health plans must provide. The definitions of accessibility and comprehensiveness depend on the meaning of the terms "medical necessity" or "medically required" used in the Canada Health Act. All ten provincial and both territorial ministries of health were contacted in the preparation of this report. None of the provinces or territories has operationally defined either of these terms.

This means that the law provides very little guidance about which services the provinces should fund. No province has a due process for deciding which services should be funded. As a result, decisions about the funding of services depend largely on the political power of various groups within the health care system. Furthermore, as documented earlier in this report, individual doctors have considerable discretion as to which services they wish to provide. In addition, there is little monitoring of their clinical practice, especially in their private offices.[115] As a result, some of the services provided are useless (or even dangerous), while some beneficial services may be completely unavailable.

For example, electronic monitoring of the fetus during labour is performed routinely in some hospitals even though experimental studies have concluded that it is useless and probably dangerous for women at low or medium risk for complications.[116] There is also high-quality scientific evidence that the provision of a trained labour attendant or "doula" can reduce the rate of complications from labour and delivery for single women.[117] However, there is at best scant provision of this service across the country.

Another barrier to a universal definition of medical necessity is that health care and illness are, at least in part, cultural constructs. Lynn Payer has documented that the French, Germans, British, and Americans have very different approaches to certain health practices and illness treatments.[118] It is commonplace for European health insurance, for example, to cover "rest cures" at health spas. In fact there is very strong evidence that relaxation and exercise can delay the onset of coronary heart disease and some other illnesses.[119]

The word "medical" refers to care by doctors, although sometimes it is misunderstood to be synonymous with "health." Some health care services delivered by non-medical personnel (non-physicians) may be very important for a person's health and therefore, arguably, medically necessary. For example, a randomized study in Wales found that the use of public health nurses reduced mortality for the elderly patients on the lists of general practitioners.[120] A Danish randomized study found that regular home visiting by public health nurses to older persons reduced mortality and rates of acute and chronic institutionalization.[121] Recently, a randomized study in New Westminster, British Columbia, found that adding a health promotion component (administered by a public health nurse) to the present long-term care assessment process for the frail elderly could markedly reduce the need for long-term care institutional services over 21 months of follow-up.[122]

There may not be easy dividing lines between services that are important for someone's health and services that simply enhance well-being. Cosmetic surgery (e.g., breast augmentation, liposuction) may improve someone's health by enhancing psychological well-being. However, this does not necessarily mean that the service is medically necessary. Most provinces do not insure plastic surgery that is strictly for cosmetic purposes. Another example is IVF. Only Ontario provides full public funding for IVF.

It seems clear that public funding cannot be provided for every service that a given doctor may feel will improve the health of an individual patient. When the medicare legislation[123] was passed by Parliament, however, the essential list of services included only medical and hospital care.[124] The medical and hospital care to be provided was what was "medically required" or "medically necessary." It is impossible to enforce these criteria without Parliament and the provinces further defining these terms.

Other Problems with Accessibility

The accessibility criterion refers to the establishment of fair procedures for deciding the remuneration of physicians. British Columbia, Newfoundland, Prince Edward Island, and the territories have not established such mechanisms.

The accessibility criterion also refers to the need for provinces to "provide for insured health services on uniform terms and conditions," which is usually interpreted as the antithesis of the approach known as

two-tiered medicine. However, this criterion could also be interpreted as requiring the establishment of standards of practice so that similar patients receive similar treatment.

Portability

The standard of portability should ensure that Canadians can receive care under similar conditions in different parts of the country. Nine provinces have signed an agreement whereby they will pay for care their residents receive in other provinces at the rates prevailing in the other provinces. Quebec has not signed this agreement. Quebec abides by the agreement for hospital bills but not physicians' services. The federal government has not penalized Quebec for this breach of the Canada Health Act.

Universality

The provinces are theoretically free to raise the money for their health programs in ways they see fit. However, there must not be financial barriers that prevent access to insured services. Alberta and British Columbia charge premiums for their health insurance plans. If a resident of one of these provinces fails to pay the premiums, he or she may not be denied services under the terms of the Canada Health Act. Rather, the province has the option of pursuing the payment of premiums through legal channels. The situation is analogous to one where someone fails to pay income taxes. Revenue Canada may take such people to court, but they may not be denied public services if they otherwise meet the criteria for receiving them.

The Hall review of medicare in 1980 and other sources[125] have suggested that some residents of these provinces are denied services because they have not paid their premiums. The federal government has not investigated this possible breach.

Penalties for Breaches

The Canada Health Act details specific penalties that may be imposed on provinces that allow their hospitals or physicians to charge user fees. The federal government deducts one dollar from their contribution for each dollar of user fee allowed within the province. However, there are no specific penalties for infringing the other program criteria of the Canada Health Act. The federal government first has discretion about whether to investigate a possible breach. Then the federal government has discretion to conclude whether there has been a breach. Finally, even if the federal government concludes that there has been a breach of one of the criteria, it has discretion about the amount of the penalty.

In conclusion, it appears the federal government is not rigorously enforcing the Canada Health Act. The accessibility and comprehensiveness criteria are so poorly defined as to be unenforceable. Quebec appears to be in breach of the portability criterion. Other provinces are in breach of the accessibility criterion because they have not developed appropriate mechanisms to negotiate with their physicians. The process for penalizing

offending provinces allows so much discretion that political exigencies could determine the federal government's response without this being obvious in any way.

The Impact of Federal-Provincial Health Care Arrangements

Because of federal cutbacks and the recession, the provinces are making their own cutbacks in funding to the providers of health care. As a result, the provinces are loath to add new services. In particular, IVF is considered by most provinces not to be "medically necessary," despite the lack of an operational definition for this term.

There are no mandatory national licensing and inspection agencies for physicians or institutions. The Royal College of Physicians and Surgeons does certify specialist physicians. These credentials are used by provincial medical insurance plans to determine remuneration for some services and by hospitals, which may restrict hospital privileges to those with certification. Authority for licensing and thus determining medical standards or guidelines[126] appears to lie with provincial licensing organizations (e.g., provincial colleges of physicians and surgeons).

It is generally believed, however, that the expertise and political balance necessary to come to consensus on standards are available only at the national level. It is not possible for a provincial college unilaterally to establish standards on IVF. When the College of Physicians and Surgeons of Ontario (the wealthiest of all the provincial licensing authorities) wished to establish standards for IVF, it sought out leaders from the SOGC and the CFAS to assist it. The lack of formal national mechanisms for establishing standards is currently hampering the development of quality assurance programs.

Health and Welfare Canada has been withdrawing its leadership on health care issues, making it less likely that national solutions will be found. Neither the Conference of Deputy Ministers nor the other statutory or voluntary agencies described earlier in this report has the staff or the mandate to coordinate the development of standards for laboratories or clinical practice.

Conclusions

New Developments in Canadian Health Policy

1. The health care system isn't nearly as important for the public's health as Canadians have come to believe.
2. The health care system is beset with a number of structural inefficiencies.
3. The public still believes that doctors and hospitals are the most important factors affecting health. The public also believes that the

health care system is operated by doctors and administrators in an efficient fashion.

4. Governments are attempting to develop broad social strategies for health and to control the costs of health care. However, they find themselves in conflict with the public and the providers of health services. The public has different values and perceptions, and doctors and hospitals have conflicting interests.

5. There is a substantial amount of inappropriate care delivered to patients by doctors and other health care providers. Doctors are poor communicators and often fail to elicit patient preferences for tests and treatments. This problem results partly from the use of fee-for-service as the principal mode of physician payment and partly from a lack of mechanisms for quality assurance.

6. The implementation of quality assurance programs can improve the quality of health care.

Changing Federal-Provincial Arrangements for Health Care

7. It isn't completely clear which level of government has jurisdiction over health policy.

8. The federal government is cutting back its financial contribution to the provinces for health care and its leadership in health policy.

9. Health and Welfare Canada has made cuts to both family planning and sexually transmitted disease control.

10. It is not clear who is responsible for elaborating clinical standards for reproductive health care. Responsibility for monitoring and enforcement of these standards is also not clear.

11. There is a leadership vacuum for the development of a national strategy for reproductive health.

12. The Canada Health Act is not being scrupulously enforced. Several provinces are in breach of the program criterion pertaining to accessibility because they have not passed appropriate legislation governing negotiations with their physicians. Quebec is in breach of the portability criterion.

13. There are no clear rules in the Canada Health Act about which services should be funded. There is no process outlined in the act for determining which services should be provided. The Canada Health Act requires provinces to cover services that are "medically required" or "medically necessary." However, no province or territory has operationally defined these terms. The provinces make their decisions about which services to fund without due process.

Recommendations

This section outlines three recommendations and then discusses the problem of the external costs of private IVF clinics.

1. There is no clear process for determining standards of practice in the Canadian health care system. If the Royal Commission wishes to ensure that standards are elaborated, then it should convene a meeting with representatives from Health and Welfare Canada, the provinces and territories, provincial medical licensing organizations, the Royal College of Physicians and Surgeons, the CMA, the CNA, consumer organizations, and other relevant groups. The Royal Commission should use the conference to help it determine a process for standards elaboration, monitoring, and enforcement.

2. At present the provinces make decisions about which health services to publicly fund on an ad hoc basis. The Canada Health Act requires the provinces to provide services that are "medically necessary" or "medically required." However, no province or territory has operationally defined these terms. The Royal Commission should recommend a national conference of governments, health care providers, and consumers to discuss a due process for determining which health services should be publicly funded.

3. There are significant barriers that obstruct the funding of programs that promote health or prevent illness. If the Royal Commission wishes to ensure that new programs are funded to prevent infertility or enhance reproductive health, it will have to make specific recommendations in this regard.

The Externalities of IVF

Professor Robert Evans of the University of British Columbia has defined an externality as follows:

> One person or organization's behaviour may affect others, independent of any voluntary transaction. My playing of loud music at night disturbs your sleep; my refusal to be immunized increases your chances of getting polio; my failure to wear seat belts increases your taxes to pay my hospital bills. Conversely my beautiful garden not only gives you pleasure, but raises your property value. Insofar as my behaviour fails to take account of such effects, because others have no way to induce me to respond to their preferences, I will (from a society-wide perspective) over-(under)indulge in activities with negative (positive) externalities.[127]

If IVF services were not fully paid for from the public purse (as is the case in nine provinces and both territories), there would still be external costs imposed on the public system. In other words, there would be at least two types of externalities to privately funded IVF.

First, there might be medical complications associated with the procedures (e.g., laparoscopy) and drugs used for IVF. For example, in the rare event that a woman suffered a heart attack while having an IVF procedure, leaving her brain dead on a respirator, the publicly funded health care system would be left to pick up costs of the treatment. There might also be significant social welfare costs involved in caring for any children she might have previously adopted or borne. In fact, one might argue that a private IVF system could not operate without the public system as a back-up.

Second, there are probably increased costs associated with children conceived through IVF. Because more than one embryo is typically implanted during an IVF cycle, the frequency of multiple births is much higher than in cases where births result from natural conception.[128] As a consequence of these multiple births, there are more Caesarian sections, more premature deliveries, and more low birthweight (less than 2 500 grams) and very low birthweight (less than 1 500 grams) babies all resulting in increased health care and social costs for the publicly funded system.

Furthermore, there are long-term effects associated with prematurity and low birthweight. A number of studies have shown that these children are much more likely than those of normal birthweight to suffer from both major[129] and more subtle physical and psychological disturbances.

Among the many methods that might be used to deal with this situation are the following:

1. ***Do nothing***
   This would result in the external costs of IVF being borne by the public sector.

2. ***Providers pay a licence fee***
   If a regulatory agency were created (as in the United Kingdom), private IVF clinics could be required to pay an annual licensing fee. The fee could be established to meet the true costs of collecting data from the facility, administering the licensing agency, and paying for the externalities of IVF.

3. ***Infertile women (couples) pay a special fee to the government for each IVF cycle***
   An actuarially-sound fee could be calculated for each cycle of IVF. The woman or couple undergoing the procedure would pay this fee to the provincial ministry of health. It should be possible to calculate the costs associated with the implantation of one, two, or three or more embryos, and the fee could vary according to the number implanted.

Option #1 is used for cosmetic plastic surgery. These procedures (with few exceptions) are not covered by public health insurance. However, they do inevitably engender complications (even with the most proficient practitioners), which result in the consumption of publicly funded health care services.

IVF is somewhat different from cosmetic surgery, however, because there are potential complications involving the children as well as the mother (the primary patient). Furthermore, the major complications for children relate to multiple births which are a result of couples' and physicians' attempts to maximize the success of the procedure. It could be argued, therefore, that the success of a commercial operation is dependent upon the existence of a publicly funded health care system. This would support the concept of a fee levied on the facility. This could vary according to the average number of embryos implanted.

Notes

1. World Health Organization, *Constitution*, 22 July 1946, in force April 1948; amended by Resolution WHA26.37, in force 3 February 1977, and Resolution WHA29.38, in force 20 January 1984.

2. Ontario, Premier's Council on Health Strategy, *A Vision of Health: Health Goals for Ontario*, (Toronto: Premier's Council, 1989).

3. World Health Organization, *Ottawa Charter for Health Promotion* (Ottawa: 1986).

4. The grants program also gave the provinces money for public health programs.

5. This act covered three "established" programs — hospital insurance, medical care, and post-secondary education.

6. Also known as the *Government Expenditures Restraint Act.*

7. This term includes family planning, pre-conception counselling, prenatal care, and obstetrical care, as well as infertility counselling and treatment.

8. Ontario, Midwifery Task Force, *Report of the Task Force on the Implementation of Midwifery in Ontario* (Toronto: 1987).

9. C. Fooks, M. Rachlis, and C. Kushner, "Concepts of Quality of Care: National Survey of Five Self-Regulating Health Professions in Canada." *Quality Assurance in Health Care* 2 (1990): 89-109.

10. C.D. Naylor, *Private Practice, Public Payment: Canadian Medicine and the Politics of Health Insurance 1911-1966*, (Montreal and Kingston: McGill-Queen's University Press, 1986).

11. The Ontario centres are funded on a program basis. The centre's operations are broken down into program budgets with staff and other expenses. In practice, program budgets function like global budgets. Some community health centres in Ontario and British Columbia are funded on capitation and some are even paid on a fee-for-service basis.

12. Ontario, *Prescriptions for Health: Report of the Pharmaceutical Inquiry of Ontario*, (Toronto: Government of Ontario, 1990).

13. Now most provinces have installed or are considering overall limits on physicians' budgets.

14. There is a long list of literature on this area. Most of the recent federal and provincial reports on health care have dealt with this issue. These reports are referenced in section entitled "Current Issues in Health Policy."

15. For example, in Ontario in the last ten years there has been a large shift in general practitioners' office visit billings from minor assessments (approximate cost, $16) to intermediate assessments (approximate cost, $23).

16. For a slightly dated discussion of these issues see: J. Lomas et al., "Paying Physicians in Canada: Minding Our Ps and Qs," *Health Affairs* 8 (1989): 80-102.

17. Canada, Health and Welfare Canada, *Achieving Health for All: A Framework for Health Promotion,* (Ottawa: 1986).

18. Ontario, Health Review Panel, *Towards a Shared Direction for Health in Ontario: Report of the Ontario Health Review Panel* (Toronto: Government of Ontario, 1987).

19. Quebec, Commission d'enquête sur les services de santé et les services sociaux. [Commission of Inquiry on Health and Social Services] *Rapport* (Quebec City: Government of Quebec, 1988).

20. New Brunswick, Commission on Selected Health Care Programs, *Report* (Fredericton: The Commission, 1989).

21. Nova Scotia, Royal Commission on Health Care, *Towards a New Strategy* (Halifax: The Commission, 1989).

22. Saskatchewan, Commission on Directions for Health Care, *Future Directions for Health Care in Saskatchewan* (Regina: The Commission, 1990).

23. Alberta, Premier's Commission on Future Health Care for Albertans, *The Rainbow Report: Our Vision of Health* (Edmonton: Premier's Commission, 1990).

24. British Columbia, Royal Commission on Health Care and Costs, *Closer to Home: The Report of the British Columbia Royal Commission on Health Care and Costs* (Victoria: Commission, 1991).

25. Canada, House of Commons, Standing Committee on Health and Welfare, Social Affairs, Seniors and the Status of Women, *The Health Care System in Canada and Its Funding: No Easy Solutions* (Ottawa: Queen's Printer for Canada, 1991).

26. Health and Welfare Canada, *Achieving Health for All.*

27. J. Lomas, "Finding Audiences, Changing Beliefs: The Structure of Research Use in Canadian Health Policy," *Journal of Health Politics, Policy and Law* 15 (1990): 525-42.

28. By 1971 all provinces had passed complementary legislation adopting the federal medicare legislation of 1966.

29. T. McKeown, *The Role of Medicine: Dream, Mirage, or Nemesis* (Princeton: Princeton University Press, 1979); R. Reves, "Declining Fertility in England and Wales as a Major Cause of the Twentieth Century Decline in Mortality: The Role of Changing Family Size and Age Structure in Infectious Disease Mortality in Infancy," *American Journal of Epidemiology* 122 (1985): 112-26.

30. J.B. McKinlay, S.M. McKinlay, and R. Beaglehole, "A Review of the Evidence Concerning the Impact of Medical Measures on Recent Mortality and in the United States," *International Journal of Health Services* 19 (1989): 181-208; A.L. Cochrane, A.S. St. Leger, and F. Moore. "Health Service 'Input' and Mortality 'Output' in

Developed Countries," *Journal of Epidemiology and Community Health* 32 (1978): 200-205.

31. World Health Organization, et al., *Ottawa Charter for Health Promotion.*

32. The Premier's Council on Health Strategy has recently been re-named the Premier's Council on Health, Well-Being, and Social Justice.

33. Ontario, Premier's Council on Health Strategy, Healthy Public Policy Committee, *Nurturing Health: A Framework on the Determinants of Health* (Toronto: Premier's Council, 1991).

34. Commission d'enquête sur les services de santé et les services sociaux, *Rapport.*

35. J.M. Moutquin and E. Papiernik, "Can We Lower the Rate of Preterm Birth?" *Journal of the Society of Obstetricians and Gynaecologists of Canada* 12 (1990): 19-20.

36. P. Wysong, " 'Preemies' Learning Handicaps May Not Show Up Until School," *Medical Post* 27 (1991): 50; S. Veen et al., "Impairments, Disabilities, and Handicaps of Very Preterm and Very-Low-Birthweight Infants at Five Years of Age," *Lancet* (6 July 1991): 33-36.

37. M.G. Marmot, "Social Inequalities in Mortality: The Social Environment," in *Class and Health: Research and Longitudinal Data*, ed. R.G. Wilkinson (London: Tavistock Publications, 1986).

38. R. Wilkins and O. Adams, *Healthfulness of Life: A Unified View of Mortality, Institutionalization, and Non-Institutional Disability in Canada* (Montreal: Institute for Research on Public Policy, 1983) R. Wilkins, G.J. Sherman, and P.A.F. Best, "Birth Outcomes and Infant Mortality by Income in Urban Canada, 1986," *Health Reports* 3 (1991): 821-26.

39. Canada, Health and Welfare Canada, *A New Perspective on the Health of Canadians*, (Ottawa: Health and Welfare Canada, 1974).

40. Health and Welfare Canada, *Achieving Health for All.*

41. New Brunswick and Ontario have adopted their health goals as government policy.

42. Ontario, Premier's Council on Health Strategy, Health Goals Committee, *Towards Health Outcomes: Goals 2 and 4: Objectives and Targets*, (Toronto: Premier's Council, 1991).

43. Québec, Ministère de la santé des services sociaux, *Improving Health and Well-Being in Québec: Orientations* (Québec: Ministère de la santé et des services sociaux, 1989).

44. R.G. Evans and G.L. Stoddart, "Producing Health, Consuming Health Care," *Social Science and Medicine* 31 (1990): 1347-63.

45. R. Proctor, "The Bitter Debate Over Health Policy," Policy Options 12 (1991): 3-7.

46. It is true that the public does show great concern for "identified victims" (e.g., a child awaiting a liver transplant) or for the health impact of environmental contaminants. However, there is little public demand for programs to prevent accidents or public concern for very dangerous but profitable products (e.g., cigarettes).

47. K.J. Fyke and B. Poole, "Doing the Right Things," *Policy Options* 12 (1991): 11-12.

48. Using Ontario data, Canada spends approximately $400 million per year on medical fees for the treatment of upper respiratory infections.

49. R.H. Brook and J.B. Kosecoff, "Competition and Quality," *Health Affairs* 7 (1988): 150-61.

50. C. Gillion, G. Scheiber, and J.P. Poullier, *Measuring Health Care 1960-1983: Expenditures, Costs, and Performance* (Paris: Organisation for Economic Cooperation and Development, 1985); E. Vayda, W.R. Mindell, and I.M. Rutkow, "A Decade of Surgery in Canada, England and Wales, and the United States," *Archives of Surgery* 117 (1982): 846-53; W.R. Mindell, E. Vayda, and B. Cardillo, "Ten-Year Trends in Canada for Selected Operations," *Canadian Medical Association Journal* 127 (1982): 123-27; E. Vayda, et al. "Five-Year Study of Surgical Rates in Ontario's Counties," *Canadian Medical Association Journal* 131 (1984): 111-15.

51. Canada, Working Group on Quality Assurance and Effectiveness in Health Care, *Report to the Conference of Deputy Ministers of Health*, (Ottawa: Health and Welfare Canada and Statistics Canada, 1990).

52. J.P. LoGerfo, "Variation in Surgical Rates: Fact vs. Fantasy," *New England Journal of Medicine* 297 (1977): 387-89; P. Diehr "Small Area Statistics: Large Statistical Problems," *American Journal of Public Health* 74 (1984): 313-14; P. Paul-Shaheen, J.D. Clark and D. Williams, "Small Area Analysis: A Review and Analysis of the North American Literature," *Journal of Health Politics, Policy and Law* 12 (1987): 741-807.

53. M.M. Cohen, et al., "Small-Area Variations: What Are They and What Do They Mean?" *Canadian Medical Association Journal* 146 (1992): 467-70; D.M. Eddy, "Variations in Physician Practice: The Role of Uncertainty," *Health Affairs* 3 (1984): 74-89.

54. R.E. Park et al., "Physician Ratings of Appropriate Indications for Six Medical and Surgical Procedures," *American Journal of Public Health* 76 (1986): 766-72. The Rand convened three panels of physicians to examine the appropriateness of six common medical and surgical procedures. The panels were selected to represent different parts of the United States, different specialties, and academic and community practice. They used a modified Delphi process to assess the appropriateness of various sets of indications for each service or procedure. The ratings were purposely biased to be conservative in the assessment of inappropriate care.

55. M.R. Chassin et al., "Does Inappropriate Use Explain Geographic Variations in the Use of Health Care Services? A Study of Three Procedures," *JAMA* 258 (1987): 2533-37.

56. P.M. Gertman and J.D. Restuccia, "The Appropriateness Evaluation Protocol: A Technique for Assessing Unnecessary Days of Hospital Care," *Medical Care* 19 (1981): 855-71; K.J. Kemper, "Medically Inappropriate Hospital Use in a Pediatric Population," *New England Journal of Medicine*, 318 (1988): 1033-37; A.L. Siu et al., "Inappropriate Use of Hospitals in a Randomized Trial of Health Insurance Plans," *New England Journal of Medicine* 315 (1986): 1259-66.

57. M.G. Taylor, H.M. Stevenson, and A.P. Williams, "Medical Perspectives on Canadian Medicare: Attitudes of Canadian Physicians to Policies and Problems of the Medical Care Insurance Program" (Toronto: York University, Institute for Behavioural Research, 1984).

58. J.E. Gloor, "Appropriateness of Admission to a Canadian Paediatric Hospital," paper presented to the Canadian Pediatric Society at annual meeting of the Royal College of Physicians and Surgeons of Canada, 20 September 1991.

59. B.J. McNeil, R. Weichselbaum, and S.G. Pauker, "Fallacy of the Five-Year Survival in Lung Cancer," *New England Journal of Medicine* 299 (1978): 1397-1401.

60. M.L. Millenson, "Video Gives Prostate Patients Reason to 'Pause,'" *Medical Post* 17 (1991): 1-5. M. Nicholson, "Interactive Video Series Benefits Patients and Doctors," *Medical Post* 27 (1991): 4.

61. L.F. Degner, J.M. Farber, and T.F. Hack, "Communication Between Cancer Patients and Health Care Professionals: An Annotated Bibliography (Toronto: Canadian Cancer Society and National Cancer Institute of Canada, 1989) K. Jenkins, "Doctors Don't Realize CA Patients Often Left in Dark," *Medical Post* 23(1987): 54; T. Murray, "Reports from International Consensus Conference on Doctor Patient Communication," *Medical Post* 27 (1991): 31-34.

62. J.E.F. Hastings et al., "Prepaid Group Practice in Sault Ste Marie, Ontario: Part I: Analysis of Utilization Records," *Medical Care* 11 (1973): 91-103; H.S. Luft, *Health Maintenance Organizations: Dimensions of Performance* (New York: John Wiley and Sons, 1981).

63. W.G. Manning et al., "A Controlled Trial of the Effect of a Prepaid Group Practice on the Use of Services," *New England Journal of Medicine* 310 (1984): 1505-10; J.E. Ware et al., "Comparison of Health Outcomes at a Health Maintenance Organization with Those of Fee-for-Service," *Lancet* (3 May 1986): 1017-22.

64. E.M. Sloss et al., "Effect of a Health Maintenance Organization on Physiologic Health: Results from a Randomized Trial," *Annals of Internal Medicine* 106 (1987): 130-38; A.R. Davies et al., "Consumer Acceptance of Prepaid and Fee-For-Service Medical Care: Results from a Randomized Controlled Trial," *Health Services Research* 21 (1986): 429-52. There were some minor differences in outcomes among subgroups. Higher income patients who started the study in poor health had slightly better health outcomes from the HMO while low income patients who started the study in poor health had slightly poorer outcomes from the HMO. Additionally, the patients allocated to the HMO were somewhat less satisfied with the care they received. This decreased satisfaction seems to have been due to patients equating increasing number of services with better quality. Finally, the study, while expensive and thorough, only investigated one HMO. Technically, the results might not apply to other non-fee-for-service organizations. However, the Group Health Cooperative of Puget Sound is non-profit and is governed by a board made up of recipients and providers of the service. In these characteristics, it resembles many of Canada's hospital boards.

65. J.E.F. Hastings et al. "Prepaid Group Practice in Sault Ste. Marie, Ontario," Saskatchewan, Department of Health, *Community Clinic Study* (Regina: Department of Health, 1983).

66. New Brunswick, Commission on Selected Health Care Programs, *Report.*

67. Nova Scotia, Royal Commission on Health Care, *Towards a New Strategy.*

68. Ontario, Health Review Panel, *Towards a Shared Direction for Health.*

69. J. Lomas, Opening remarks for the International Conference on Quality Assurance and Effectiveness in Health Care, Toronto, November 1989.

70. G. Anderson and J. Lomas, "The Development of Utilization Analysis: How, Why and Where It's Going," in *Reviewing Utilization: The Methods and Promise of Utilization Analysis for the Canadian Health Care System*, ed. C. Fooks and J. Lomas (Hamilton: McMaster University, Department of Clinical Epidemiology and Biostatics, Centre for Health Economics and Policy Analysis, 1988).

71. Efficacy deals with the question of whether something works under ideal circumstances. Effectiveness deals with the question of whether something can work under "real world" circumstances.

72. See an overview of the science system prepared for the Royal Commission by R. Voyer and L. Edwards for more details about the technology assessment process.

73. A physician could be liable if the drug caused an adverse event when prescribed for an unapproved indication, but this happens rarely, if ever.

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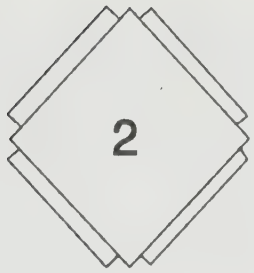
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Framework for Technology Decisions: Literature Review

Arminée Kazanjian and Karen Cardiff



Executive Summary

Decisions on health care funding of new technologies have been partisan, fragmented, and ad hoc. Development, diffusion, and ultimately accessibility are accountable to society at large concerning equity, social and ethical impact, and allocation of increasingly limited financial resources.

Mechanisms exist to control diffusion of expensive technologies (e.g., fee-for-service schedules); however, assessment of the technologies, and their various effects, has followed their development. Once assessment does begin, it is unrealistic to assume that development and diffusion of technologies will pause till the results are in.

In the context of the need for evaluation of technology that would take into account the complexities of development within an ongoing social context, that would consider equity, economic, legal and ethical as well as political components, the present study was timely and appropriate. The object of the study was to provide a critical appraisal of a health technology decision model. The model, with social components encompassing population at risk, population impact, costs, technology assessment, and ethical/ legal/social/political implications, was intended to offer an empirical foundation to assess technology decisions.

This paper was completed for the Royal Commission on New Reproductive Technologies in May 1992.

The method of study involved, first of all, an extensive multidisciplinary literature search using North American and European data bases. This revealed over 1 300 related articles. From these, 173 directly related studies were examined in depth to test the model and assess the status of the literature. The model's key dimensions were applied to 173 studies of health care decision making.

Included in the evaluation was a tabular measure of articles from a theoretical/analytical, empirical, or editorial/ personal viewpoint. Only five percent of the articles were empirically based. More such work needs to be undertaken to determine how decisions regarding public policy should be made to better serve the public interest. Another section of general comment regarding the technical feasibility of developing a mathematical model based on the suggested conceptual model ends the paper.

Introduction

Decisions regarding technology are made daily by practitioners, administrators, and policy makers. Ideally, decisions regarding health technology should be based on evidence from comprehensive assessment — that is, information on the safety, effectiveness, costs, and ethical, legal, and social implications of the particular technology under consideration. Reality proves otherwise; the large majority of technological innovations in health care are in use long before any systematic assessment has taken place. Sometimes, at the second- or third-generation level, technologies are found to be ineffective, or even unsafe, after belated assessment. The Canadian Standards Association tests medical devices for safety, and the Canadian Food and Drug Administration polices the safety testing of pharmaceutical products (acting as the regulator). However, the effectiveness studies made available to health care providers are usually undertaken by the research staff of the manufacturer or the pharmaceutical company. There is thus a serious conflict of interest that compromises the credibility of the evidence.

The role governments play in the development and diffusion of technology is clearly an influential one, especially in health care. It spans a wide range of levels of involvement — from supporting the development of technologies through funding of research in basic sciences, to regulating the marketing of certain technologies and licensing of facilities for the provision of certain technological services, to paying for such services through public funds (medical insurance). Yet these policy decisions are most often made in the absence of accurate information on the specific as well as general implications of such technological development or diffusion.

Background

Decisions about who will get how much of what in health care are made mostly in an ad hoc fashion, with different motives operating for the different levels of decision makers. Although some mechanisms exist for influencing technological adoption and diffusion, such as regulation under special programs for the purchase of expensive technologies (Deber et al. 1988) or fee-for-service schedules that signal what services can be provided and how much the payment will be (Evans 1982), policy mechanisms at present are neither coordinated nor applied consistently to ensure predefined and publicly articulated health goals. Moreover, prospective assessment of the consequences of technology decisions has not been part of the decision-making process.

The determination of whether decisions pertaining to new reproductive technologies are more rationalized than decisions for other health technologies is an important research question, but one beyond the scope of the present study. The popular assumption, however, is that the consequences — especially ethical — of new reproductive technologies are potentially more serious than those of the average health technology decision. Therefore, an understanding of how allocative decisions regarding resources for medical technology in general are made would be extremely helpful in understanding specific decisions regarding reproductive technologies.

Although it would be prohibitive to undertake extensive technology assessment work every time a resource allocation or other policy decision had to be made, it would be desirable to make decisions based on informed judgments about the clinical, fiscal, and social impact of health technology before it is widely adopted and extensively used. Thus, in a pilot study on technology adoption and diffusion (Kazanjian and Friesen 1990), the present authors examined the feasibility of developing a taxonomy to classify emerging and existing technologies. Taxonomy involves identification of an object, recognition of its specific limits, placing it within its natural groups, and constructing classifications that as near as possible show the course of evolution within a group (Cain 1959). We reviewed a vast and rapidly increasing literature in the area of technology assessment and, in a more limited fashion, the clinical literature pertaining to two broad categories — laboratory tests and imaging devices — and also the literature on taxonomy development. Part of the conclusion from that study was that neither the inherent characteristics of health care technologies nor their assumed properties lend themselves to taxonomic classification. The decision maker confronted with an allocation or other technology decision has very little use for the highly technical information specific to the attributes of one or another technology; a decision tool was needed to quantify the relative merits of technologies under consideration.

Framework for Technology Decisions

Confronted with a choice among several technologies, the policy maker has a number of possible alternatives (Churchill 1987):

1. refuse to consider the particular merits of each technology, and simply divide the resources equally so that each gets equal shares of (most likely) inadequate resources;
2. consider resource requirements of each technology and give each an equal percentage of its request so that relative resource requirements are allocated to all;
3. choose technology that will assist the neediest or the most ill, that is, technology that would seek to rescue those nearest to death;
4. choose technology that promises long-range efficiency and effectiveness, that is, a technology that does not entail expensive or ineffective rescue efforts;
5. choose technology that will effectively help the largest number of persons, that is, technology that seeks the greatest good for the greatest number;
6. choose the technology of greatest value to those whose condition is caused or exacerbated by previous social or economic injustices — that is, use the principle of restorative justice;
7. choose technology of service to those who have previously been treated or to whom one owes fidelity due to past obligations — that is, honour long-standing obligations; and
8. use the lottery approach and draw the "winner" from a hat.

Given the high stakes involved, in the sense that the entire population in a jurisdiction is affected by government policy decisions, selecting an alternative that includes equity and utility and is also grounded in principles of social justice seems the most appropriate. A decision framework that reflects these attributes and rationalizes choices between technologies in terms of equity and utility is arguably more useful than a priority classification scheme that is divorced from considerations of health consequences of the technology.

The rationale for the development of our health technology decision framework was centred on principles of justice in health care: *equitable access to all effective health care that society can afford.* That the decision maker employs norms of utility as well as equity in making a decision is implied. Neither of these lends itself to easy formulation of policy. Some adjudication and interpretation is needed to translate principles into action; how much technology and for whom?

The practitioner is most motivated by clinical efficacy, the administrator by fiscal and other resource implications that affect quality of care, and the government agency by budgetary restrictions (i.e., economic efficiency). Although each is engaged in what would be considered proper or ethical behaviour, all of the above behaviours are based on principles of ethical individualism that are deeply rooted in North American culture (Churchill 1987). Such principles are operant in all Canadian health care decision making.

The individual and society cannot be treated separately, or given different moral priorities, because they are complementary realities. Individuals develop a socially defined sense of selfhood, in which no one person has a prior entitlement to health (services) based on social differences. However, given society's finite resources, an equitable health system is concerned with the provision of effective care it can reasonably afford. Such a perspective for the provision of health services rests on basic principles of social justice pertaining to the collective welfare of society.

Using the humanist perspective as theoretical underpinning, and the empirical evidence from our previous pilot study indicating the futility of any attempt to consistently link either inherent attributes of the technology to its diffusion, or health care technology diffusion to the prevalence of disease, a preliminary decision framework was developed using five key dimensions (Table 1). The first four — population at risk, population impact, costs, and ethical/legal/social/political implications — are societal responses to the particular technologies of concern. The fifth component, technology assessment activity, is a descriptive element included to provide a "quality of medical knowledge" perspective, incorporating information on the quality of the assessment evidence and its degree of convergence.

The purpose of such a conceptual model is to provide an empirical, evidence-based foundation to technology decisions, demystifying a heretofore undefined and generally misunderstood phenomenon.

The term "population at risk" takes into account the magnitude of the health concern related to the technologies, indicated by prevalence, severity of illness, and other such epidemiologic measures in that jurisdiction. For example, acquired immunodeficiency syndrome (AIDS) affects a relatively small proportion of the population (prevalence), but its effect is fatal (severity); in comparison, arthritis affects a much larger proportion of people, but the debilitating effects are generally mild to moderate or severe.

"Population impact" takes into account the known expected health consequences of the technological intervention indicated by comprehensive general health status measures. Although a person suffering from heart disease will experience various levels of functional disability, a person diagnosed HIV (human immunodeficiency virus) positive may have years of symptom-free and disability-free existence. Thus, a measure of the change in quality of life over the life expectancy of the respective cohorts affected by each of the technologies provides another policy component. This second dimension of the framework, combined with the first (population at

risk), expresses considerations of utility — the greatest good for the greatest number — the selection being made *not* between individuals but among categories of health concerns.

The cost component of the decision framework includes what society can reasonably afford. Aggregate costs of each of the technologies, costs of alternatives to the technologies and more specific measures of costs per well-year of life are possible measures of fiscal implications. The answer to the question of how society arrives at decisions about what it can afford is a very important but opaque one. How a government agency arrives at that same decision appears to be somewhat less opaque. Finite financial resources set the parameters; principles of distributive justice serve to eliminate any social ordering. Yet even here, public perception and special-interest lobbying affect decisions.

No rational health technology policy decision can be taken without at least cursory consideration of the social, political, ethical, and legal ramifications of that decision. Although it may be possible to clearly delineate legal implications, the other three aspects are not so clearly identifiable. However, the weight carried by political considerations may be enormous. Rational decisions would be made by weighing the political consequences of making a choice versus not making that choice. Social implications are generally more difficult to define than the political, and less likely to incite prompt government action, yet they tend to yield longer-term consequences and can be considerably more serious than any of the others. Perhaps the least well understood, and therefore the most neglected, sub-component is ethical consequences of health technology decisions. Although the field of bioethics is acquiring a higher profile, ethical considerations are not routinely incorporated in official guidelines or protocols for deciding about health technologies.

The final component, technology assessment activity, is different from the other four in that it indicates the level of scientific knowledge that acts as backdrop to the decision. Whereas most of the research in technology diffusion assumes that the mere existence of technology assessment will influence diffusion, it generally fails to separate the three levels of stakeholders in technology assessment (Fodor 1988; McGivney and Schneider 1988; Peddecord et al. 1988). Physicians, facility administrators, and government officials look to technology assessment for different reasons and, therefore, assessment has a different function for each of the groups. (The role of the public is omitted from this discussion for the sake of brevity.) New information from technology assessment may affect physicians' clinical behaviour, could help the administrator in acquisition decisions, and should assist the government agency in reimbursement or regulatory policy making.

Table 1. Matrix for Decisions on Health Technology

Dimension	Method(s)	Tool(s)	Source(s)
POPULATION AT RISK (of problem/disease/ health issue)	Epidemiologic orientation	Natural history/severity of illness scale	Clinical epidemiology literature
	Descriptive epidemiology	Incidence/prevalence rates, mortality rates	Administrative data bases (from vital statistics, HMRI, MSP, census surveys, etc.)
	Indices of community health	Life expectancy, social deviance, summary index	
POPULATION IMPACT (of problem/disease/ health issue)	Health status measures	i) Functional assessment inventory	Crewe & Athelstan (1981)
		ii) Sickness impact profile	Bergner et al. (1981)
		iii) Nottingham Health Profile	Hunt et al. (1981)
		iv) Quality of well-being scale	Kaplan & Anderson (1988)
COST	Economic analysis of net cost to the health care system	i) Aggregate cost ii) Cost of alternatives iii) Cost-utility analysis	Standard measures Data bases (MSP, HS1, HS2, HMRI)

Table 1. (*cont'd*)

Dimension	Method(s)	Tool(s)	Source(s)
ETHICAL/LEGAL/SOCIAL/ POLITICAL IMPLICATIONS	Descriptive synthesis of issues from literature Local situation	Score for current or potential importance of issue (on Likert-type scale)	International journals/experts Local experts Media coverage Lobby groups
TECHNOLOGY ASSESSMENT ACTIVITY	Framework of major emphasis of technology assessment activities	i) Score for comprehensiveness of assessment activity ii) Score for congruity of findings	Institute of Medicine (1985)

HMRI - Health medical records institute
MSP - Medical services plan
HS1 - Hospital statistics 1
HS2 - Hospital statistics 2

The temporal order of evaluation-decision is also very different for each of the stakeholders. For the policy maker, ideally the assessment should precede policy formulation. In actuality, it rarely, if ever, does. For the administrator, the information is sought only when it affects that particular institution. For the physician, the information is useful when it affects medical practice. It makes sense that clinical evaluation of medical and surgical procedures should precede their widespread use. This order also holds true for regulatory bodies such as the Canadian Standards Association and Canadian Food and Drug Administration, whose mandate is to establish safety and efficacy before releasing devices and drugs. But it does not make sense to suggest that all government financing and insurance coverage policies should be based on locally undertaken primary assessment of each technology when that information may already exist in other jurisdictions (Davis 1986).

There are ten identified sources of influence in the adoption or abandonment of health technology (Institute of Medicine 1985), of which environmental constraints and incentives are the major ones susceptible to policy influence. It may therefore be more efficient for the policy maker to develop such incentive and disincentive policies first, based on a synthetic evaluation of available knowledge, and subsequently call for more serious primary assessment efforts, if required. It is unrealistic to believe that technology diffusion would stop while extensive evaluation is undertaken. The last dimension of the decision framework, technology assessment activity, is used to qualify the four preceding components and alerts the policy maker to the relative assessment status of each technology.

Objective and Scope of Study

The objective of the present study was to provide a critical appraisal of the literature on each of the dimensions developed in the preliminary health technology decision model. We anticipate this model could ultimately provide a framework to analyze decision making pertaining to the allocation of resources for health technologies. A critical appraisal of the literature examined the quality and volume of the evidence pertaining to the conceptual model, establishing the feasibility of its empirical application. In addition, the literature review delineated the evidence on how decision-making processes evolve and on what type of information is sought by persons making clinical, administrative, or public policy decisions.

Although beyond the scope of the present study, the extension of such work would lead to the development of quantitative measures — new or already existing — that could be combined to develop a mathematical model to estimate "global scores" for health technologies under consideration when decisions necessitating choices between technologies

must be made. The purpose of a mathematical model, once developed, would be to facilitate the ways in which global scores can be applied to establish priorities. Such measures would indicate the broader socio-medical value of technologies which, although unrelated, may be competing for the same limited resources.

Methodology

The literature review proceeded in four phases. The first phase involved identifying relevant sources of information on literature related to decision making in health care. To do this, librarians from a variety of disciplines were contacted and interviewed to determine which data bases would yield comprehensive and relevant results. Fifteen data bases representing social science, biomedical, scientific, feminist[1] and business literature were recommended. Twelve of these are North American data bases and include the following: ABI/INFORM; US Political Science Documents; Management Contents; Economic Literature Index; PAIS International; Sociological Abstracts; MEDLINE; Health Planning and Administration; Biobusiness; NTIS; MATHSCI; and Health Periodicals Database. The other three data bases are European and include: FRANCIS; PASCAL; and Bioethics. A concise description of each data base follows.

North American Data Bases

ABI/INFORM

ABI/INFORM contains more than 480 000 citations, with abstracts, to the periodical literature of business and management. It covers over 800 international periodicals in these subject areas: accounting and auditing; economics; electronic data processing systems and information science; engineering management; finance and financial management; health care; law and taxation; management science; marketing; advertising and sales management; personnel, employee benefits, and labour relations; banking; insurance; public administration and government.

A hierarchical classification system allows users to create broad topical subsets before applying specific search terms. Five areas are covered by the classification codes: business environment (e.g., economic conditions, social policy); management function (e.g., public relations, planning, information management); industries and markets; article treatment (e.g., company-specific, product-specific); and what the organization does (e.g., small business, non-profit institution).

US POLITICAL SCIENCE DOCUMENTS

This data base provides detailed abstracts and indexing from approximately 150 of the major American journals publishing scholarly articles in the broad area of political science. Coverage includes such specific areas as: foreign policy; international relations; behavioural sciences; public administration; economics; law and contemporary problems; world politics; and all areas of political science, including theory and methodology. This data base is of particular interest to the academic community, providing a central source from which to access significant research results in the political, social, and policy sciences.

MANAGEMENT CONTENTS

The Management Contents data base provides current information on a variety of business- and management-related topics to aid individuals in business, consulting firms, educational institutions, government agencies, government bureaus, and libraries in decision making and forecasting. Articles from over 140 U.S. and international journals, as well as conference proceedings, transactions, business course materials, newsletters, and research reports are fully indexed and abstracted to provide up-to-date information in the areas of: finance and economics (including accounting, banking, and managerial economics); industry (including commodities and goods, production, and industrial relations); and management and administration (including public administration, planning, decision science, human resource development, management philosophy, operations research, and marketing).

ECONOMIC LITERATURE INDEX

The Economic Literature Index is an index of journal articles and book reviews from 300 economics journals and from approximately 200 monographs per year. It covers: general economic theory, history, and systems; economic growth, development, planning, and fluctuations; quantitative economic methods and data; international economics; domestic monetary and financial theory and institutions; administration, business finance, marketing, and accounting; industrial organization, technological change, and industry studies; agriculture and natural resources; manpower, labour, and population; welfare programs; consumer economics; and urban and regional economics. Since June 1984, abstracts from selected journals have been added to approximately 25 percent of the records in the file. The descriptive abstracts are approximately 100 words in length and are written by the author or editor of the journal article; all are in English. The data base corresponds to the index section of the quarterly *Journal of Economic Literature* and to the annual *Index of Economic Articles.*

PAIS INTERNATIONAL

PAIS International is a U.S.-based bibliographic index to the public policy literature of business, economics, finance, law, international relations, government, social sciences and political issues, and the making and evaluating of public policy. It provides references in English to material published worldwide in any of six languages: English; French; German; Italian; Portuguese; and Spanish. Approximately 60 percent of the items indexed were originally published in English. It covers printed material in all formats: periodical articles; books; state, local, federal, and non-U.S. government documents; committee hearings; pamphlets; and the reports of public and private organizations. PAIS International provides comprehensive coverage of all issues of public policy relating to social, economic, or political problems, including: taxation; multinational corporations; banking; labour; insurance; crime; health; international relations; international trade; and specific industries. It is an enhanced compilation of two print publications: PAIS Bulletin and *PAIS Foreign Language Index.*

SOCIOLOGICAL ABSTRACTS

Sociological Abstracts covers the world's literature in sociology and related disciplines in the social and behavioural sciences. Over 1 600 journals and other serial publications are scanned each year to provide coverage of original research, reviews, discussions, monographic publications, panel discussions, case studies, conference papers, and dissertations.

MEDLINE

MEDLINE, produced by the U.S. National Library of Medicine, provides access to worldwide biomedical literature, including research, clinical practice, administration, policy issues, and health care services. MEDLINE corresponds to three print indexes: *Index Medicus*; *Index to Dental Literature*; and *International Nursing Index.* MEDLINE covers virtually every subject in the broad field of biomedicine, indexing articles from over 3 000 international journals published in the United States and 70 other countries. Citations to chapters or articles from selected monographs are also included from May 1976 through 1981.

HEALTH PLANNING AND ADMINISTRATION

Health Planning and Administration, produced by the U.S. National Library of Medicine, contains approximately 500 000 citations to the worldwide literature on health care delivery. It covers: health care planning and facilities; health insurance; and the aspects of financial management, personnel administration, manpower planning, and licensure and accreditation that apply to the delivery of health care. References in Health Planning and Administration are drawn in part from MEDLINE and from the American Hospital Association's *Hospital Literature Index.* Documents from the National Health Planning Information Center are

included, as well as additional journals of special importance to the health care field.

BIOBUSINESS

Biobusiness contains approximately 164 000 citations, with abstracts, to the worldwide periodical literature on business applications of biological and biomedical research. It covers: agriculture and forestry; food technology; genetic engineering; pharmaceutical products; and other industries affected by biotechnological developments. It also covers patents in such areas as: immunological testing; food processing; and fishing. Each patent record includes: inventor's name and address; patent title and number; patent classes; date granted; and assignee. Sources are journals, books, newsletters, monographs, and conference proceedings.

NTIS

NTIS contains approximately 1.4 million citations, most with abstracts, to unrestricted technical reports from U.S. and non-U.S. government-sponsored research, development, and engineering analyses. The unpublished U.S. reports are prepared by federal, state, and local agencies and their contractors or grantees. Major areas covered include: the biological, social, and physical sciences; mathematics; engineering; and business information. The data base includes: announcements of computer-readable software and data files; U.S. government-owned inventions available for licensing; selected reprints; federally sponsored translations; and non-English-language reports. It corresponds to the biweekly publication *Government Reports Announcement & Index* and, in part, to the weekly *Abstract Newsletters*.

MATHSCI

MATHSCI contains evaluative reviews and abstracts of the international research literature in mathematics, computer science, statistics, econometrics, and applications in areas such as physics, engineering, biology, and information systems. MATHSCI has seven subfiles on-line: *Mathematical Reviews* and *Current Mathematical Publications*, published by the American Mathematical Society; *ACM Guide to Computing Literature* and *Computing Reviews*, published by the Association for Computing Machinery; *Technical Reports in Computer Science*, compiled by Stanford University; *Current Index to Statistics*, published by the American Statistical Association and Institute of Mathematical Statistics; and *Index to Statistics and Probability* (Tukey), by Tukey and Ross. The combined coverage of the seven subfiles is very comprehensive. Approximately 600 journals are reviewed from cover to cover and 2 500 journals are examined selectively. In addition, over 10 000 monographs, conference proceedings, theses, and technical reports are reviewed annually.

HEALTH PERIODICALS DATABASE

Health Periodicals Database provides indexing and full text of journals covering a broad range of health subjects and issues. Subjects include: prenatal care; dieting; drug abuse; AIDS; biotechnology; cardiovascular disease; environment; public health; safety; paramedical professions; sports medicine; substance abuse; toxicology; and much more. Articles are collected from core health, fitness, and nutrition publications. The data base provides a valuable resource for: corporate; medical; and legal librarians; human resources professionals; and product analysts.

CUADRA

The CUADRA data base contains descriptions of about 5 000 data bases worldwide, including over 4 500 on-line data bases and over 950 portable ones (i.e., data bases available on CD-ROM, diskette, and magnetic tape).

Each entry provides: the data base name; classification (Audio, Bibliographic, Full Text, Full Text/Images, Images, Numeric, Referral, Software, Textual-Numeric, Video); data base producer or information provider; on-line services or vendors through which the data base can be accessed or purchased; content description; subject; language; geographic coverage; time span; frequency of updating; and, as applicable, conditions of access or price. For portable data bases, CUADRA also covers: format (e.g., High Sierra or ISO 9660 for CD-ROMs, number and size for diskettes): hardware and software requirements; and corresponding on-line and printed information sources. CUADRA includes addresses and contact numbers for data base producers and information providers and for on-line services or vendors. It corresponds to the printed *Directory of Online Databases* and *Directory of Portable Databases*.

European Data Bases

FRANCIS

FRANCIS is a leading bibliographical data base of the human, social, and economic sciences. Coverage includes both the human sciences and the social sciences. The data base language is French, with English, German, and Spanish descriptors.

BIOETHICS

This is an international data base on biomedical ethics, including: coverage of health policy; neonatology; doctor-patient relationships; reproductive contraception; abortion; reproductive technology; genetic engineering; experiments on humans; artificial and implanted tissue; and problems related to death and violence. The data base is in English and French.

PASCAL

PASCAL contains about 8 million citations, with abstracts, to the worldwide literature in science, technology and medicine. It covers: applied science; biomedicine; chemistry; computer science; earth sciences; engineering; fundamental and applied biology; marine science; mathematics; medicine; physics; psychology; and space science. Sources include: books; theses; reports; conference proceedings; and more than 4 500 periodicals.

Literature Review

During the second phase of the review, lists of key words were created, using the controlled vocabulary of the respective data bases. Next, search strategies for each data base were developed. Following from this, extensive searches were executed using Boolean logic.[2] It should be pointed out that the terms *decision making*, *health policy* and *public policy* are the subject of many literatures; to ensure the applicability of the literature to the needs of this study, the authors limited searching to articles where decision making, health policy, and public policy were the focus of the article. (Please see Appendix 1 for details of the search strategies and the results of searches for 10 data bases.) The final stage of the literature review involved selection of relevant articles and critical appraisal, which considered a variety of factors including: theoretical grounding; empirical evidence; methodological rigour; clarity of findings; and convergence of findings with other work.

Results

The literature review yielded approximately 1 300 abstracts related to decision making in health care (after overlap in articles was eliminated). Tables 2 to 4 outline the results from three of the data base searches. In Table 2 the results from the search of ABI/INFORM indicate that, though there were a total of 28 214 articles with a focus on decision making, only 1 502 (5%) of the articles were related to decision making in health care. In Table 3 the results from the search of MEDLINE show there were 3 658 articles related to decision making or policy, and the results from the Health Planning and Administration data base search (Table 4) reveal 5 434 articles related to decision making or policy.

Table 2. ABI/INFORM Data Base Search

Data base	Search word(s)	No. of articles
ABI/INFORM (1986 - Nov. 1991)	Decision/policy	28 214
	Decision/policy related to health care	1 502
	Decision/policy related to health care 'and' population health/population impact	149
	Decision/policy related to health care 'and' economics	61
	Decision/policy related to health care 'and' technology assessment	48
	Decision/policy related to health care 'and' law	200
	Decision/policy related to health care 'and' politics	29
	Decision/policy related to health care 'and' ethics	28

Table 3. MEDLINE Data Base Search

Data base	Search word(s)	No. of articles
MEDLINE (1987 - Jan. 1992)	Decision/policy	3 658
	Decision/policy related to delivery of health care	33
	Decision/policy related to costs/cost benefit analysis	107
	Decision/policy related to health	16
	Decision/policy related to health care rationing	43
	Decision/policy related to health facilities	19
	Decision/policy related to health planning (search limited to 1990-92)	17
	Decision/Policy related to health priorities (search limited to 1990-92)	11

Table 3. (*cont'd*)

Data base	Search word(s)	No. of articles
	Decision/policy related to health resources (search limited to 1990-92)	19
	Decision/policy related to health services (search limited to 1990-92)	26
	Decision/policy related to health services research	35
	Decision/policy related to health status indicators (search limited to 1990-92)	14
	Decision/policy related to health surveys	16
	Decision/policy related to technology assessment	50
	Decision/policy related to population surveillance	4
	Decision/policy related to medical ethics	149

Table 4. Health Planning and Administration Data Base Search*

Data base	Search word(s)	No. of articles
Health Data Base (1975 - Jan. 1992)	Decision/policy	5 434
	Decision/policy related to delivery of health care	33
	Decision/policy related to costs/cost benefit analysis	69
	Decision/policy related to health	14
	Decision/policy related to health care rationing	11
	Decision/policy related to health care facilities	11
	Decision/Policy related to health priorities (search limited to 1990-92)	16
	Decision/policy related to health resources (search limited to 1990-92)	25

Table 4. (*cont'd*)

Data base	Search word(s)	No. of articles
	Decision/policy related to health services (search limited to 1990-92)	4
	Decision/policy related to health services research	27
	Decision/policy related to health status indicators (search limited to 1990-92)	4
	Decision/policy related to health surveys	4
	Decision/policy related to technology assessment	49
	Decision/policy related to population surveillance	8
	Decision/policy related to medical ethics	25

* Overlap between Health data base and MEDLINE was eliminated in this search.

Descriptive Analysis

Although 1 300 abstracts were reviewed, only a small proportion (13%) were actually relevant to the particular focus of the study. These 13% (173 articles) were examined in depth (see Table 5). Entire articles were retrieved for the most part (160 articles); however, in 13 of the cases the authors only had access to abstracts.

Articles were categorized as either theoretical/analytical, editorial/personal viewpoint, or empirical. Approximately 51% of the articles were theoretical/analytical in nature; 44% were editorial or personal viewpoints (Table 5 shows data, article by article); 5% of the articles were empirically based. With respect to focus, it should be pointed out that most of the literature addressed more than one dimension, as follows: 55 of the articles (32%) discussed the role of economics; 88 of the articles (51%) discussed the role of ethics/equity; 42 of the articles (24%) discussed the role of political and legal factors; 57 of the articles (33%) discussed the role of social factors; 41 (24%) of the articles discussed the role of epidemiologic factors (population at risk, population impact); and 54 (31%) of the articles discussed the role of technology assessment activities.

Table 5. Analysis of Articles Reviewed

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Aaron & Schwartz (1990)	P					
Adams (1988)			P			
Allen (1991)		P		P		
American Medical Association (1991)		E		E		
Balk (1990)		T		T		
Banta & Andreasen (1990)						T
Banta et al. (1987)						T
Battista (1989)						T
Begin (1989)		T	T	T		
Behrens & Henke (1988)	P					
Benjamin (1990)		T				
Berman et al. (1990)						P
Berwick (1988)	P					
Binney & Estes (1988)		T		T		
Björk & Rosén (1991)		P				
Blank (1984)						T
Blank (1988)						T
Bloche & Cournos (1990)	T	T	T	T	T	
Blumstein (1976)			T			
Bowie (1991)	P					

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Bozeman & Rossini (1979)						T
Brehm & Mullner (1989)						T
Brody (1988)		P		P	P	
Brody et al. (1991)	E					
Brown (1991)	T	T		T	T	T
Bucci (1991)						P
Burt (1977)			P			
Callahan (1988)	P	P		P	P	P
Callahan (1991)		P		P		
Calltorp (1988)						E
Capron (1989)		P	P	P		
Chana & Lundstrom (1990)		P		P		
Chapman (1985)	P	P				
Connelly (1991)		P	P	P		
Crane (1988)					T	
Crichton (1989)		T				
Danis & Churchill (1991)		T		T		
Deber & Goel (1990)		T		T		
Deber et al. (1988)			T			T
Detsky & Naglie (1990)	T	T	T			
de Wachter (1988)		T				
Drane (1988)	T	T	T	T	T	

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Drummond (1987a)	T				T	
Drummond (1987b)					P	
Drummond (1989)		T			T	
Drummond (1990)	T					
Duff & Campbell (1980)		P		P		
Duggan (1989)	P	P	P		P	
Eddy (1990a)						P
Eddy (1990b)	P					
Eddy (1990c)	P		P	P		
Eddy (1991a)		P		P		
Eddy (1991b)	P	P		P	P	
Eddy (1991c)	P	P		P	P	
Eisenberg (1989)	T					
Ellencweig (1988)						T
Emery & Schneiderman (1989)	T	T				
Emson (1991)	P	P	P			P
Etzioni (1975)		P		P		
Etzioni (1991)	P	P			P	
Evans (1990)			T	T		
Evans (1983)		T				
Feeny & Stoddart (1988)						T
Feldstein (1990)	T	T	T	T		
Fox & Leichter (1991)		T		T		T

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
France (1988)						T
Friedman (1987)		P		P		
Friedman (1989)		P				
Fuchs & Barber (1990)						P
Gafni (1991)	T					
Garber & Wagner (1991)	T				T	T
Gemmette (1991)		T	T	T		
Ginzberg (1982)						P
Goldberg (1988)		E	E	E	E	
Golding (1984)						P
Grannemann (1991)		T	T			T
Gula (1990)		T	T	T		
Haan (1991)	T	T		T		
Hadorn (1991a)	T	T	T	T	T	
Hadorn (1991b)				T	T	
Hakulinen & Hakama (1991)					T	
Halstead et al. (1991)						T
Hayry (1991)					T	
Ikegami (1988)						T
Jacobson & Rosenquist (1988)						T
Jennett (1988a)	T	T				
Jennett (1988b)						T

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Kaplan & Anderson (1988)					T	
Kelly (1990)	P	P	P			
Kelsey (1975)	P	P	P	P	P	
Kilner (1988)		T		T	T	
King (1990)		P				
Klein (1989)						P
Klein (1990)						T
Koska (1991)						P
Krahn & Detsky (1992)	P				P	
Lamm (1987)		P		P		
Lamm (1989)						P
Lamm (1990)						P
Lan (1987)						T
Larson (1989)						T
Laupacis (1992)	T	T	T			
Levey (1990)						P
Levkoff & Wetle (1989)		E		E	E	
Lomas (1990)						T
Loomes & McKenzie (1989)					T	
Maher (1991)	T	T				
Marmor (1990)		P				
McCormack (1988)		T	T	T		

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
McGivney & Schneider (1988)						T
Mechanic (1976)		P		P		
Mechanic (1989)		P	P	P	P	
Menzel (1990)		T				
Molloy et al. (1991)	E	E	E		E	
Momeyer (1990)		T				
Morey (1988)		P				
Murphy & Matchar (1990)	T	T		T	T	
Myers (1977)		P				
Natiello (1988)	P					P
Neuhauser & Napier (1989)						P
O'Malley (1991)		E		E		
Omenn (1990)	T				T	
Oster (1988)	T					
Paris & O'Connell (1991)	P	P	P	P	P	
Parker (1990)						T
Peña-Mohr (1987)						T
Read (1990)	P	P		P		
Reagan (1989)		P				
Reiser (1992)			T	T		
Relman (1990)						P
Rettig (1989)		T				T

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Reynolds (1989)	T	T	T	T	T	
Rice (1989)	T				T	
Rodin & Collins (1991)		T	T	T	T	
Ross (1991)	P	P	P	P		
Rossiter (1990)	P					
Rothschild (1990)			P			
Russell & Sisk (1988)						T
Rutten & Banta (1988)						T
Sabatino (1991)		P			P	
Salter (1991)	P	P	P	P	P	
Schweitzer (1990)						P
Shannon (1987)		P		P		
Sidel (1987)		P				
Siegler (1985)	P	P		P		
Sisk (1987)						P
Smith (1989)	P	P		P		
Starr (1975)				P		
Steinwachs (1989)					T	
Svanström (1988)		P				
Tanneberger (1988)						T
Thompson & Milunsky (1979)	T	T	T			
Tokarski (1990)			P			
Torrance (1987)	T					

Table 5. (*cont'd*)

Author(s)	Economic	Ethical/ equity	Legal/ political	Social	Epidemi- ologic	Tech- nology assess- ment
Tugwell et al. (1986)						T
Tymstra (1989)				T		
Vilnius & Dandoy (1990)	T	T	T		T	
Wagstaff (1991)		T			T	
Weinstein (1989)	T				T	
Weinstein (1990)	T					
Weinstein and Stason (1977)	P	P	P			
Wennberg (1990)						P
Wetle et al. (1988)			E	E	E	
White (1989)		P				P
Wikler (1991)		T				
Williams (1987)	P	P	P	P	P	
Williams (1988)		T	T	T		
Wissema (1981)						P
Wray et al. (1988)		E		E		
Wright (1991)		T				
Zajac (1989)			P			
Zeckhauser & Shepard (1976)	T	T	T			
Ziporyn (1983)						P

Legend:
T = Theoretical/Analytical
P = Personal Viewpoint/Editorial
E = Empirical

Convergence of Findings

It appears to be a consensus statement that rational analysis and systematic planning ought to be the norms governing health technology decisions. There is appreciable convergence of research findings regarding the desirability of a rational approach to policy decisions pertaining to health technologies, regardless of source, disciplinary perspective, or methodology. Some differences emerge, however, when the criteria and/or factors that constitute the focus of rational planning are considered. The proposed technology decision framework was used to provide focus to the critical appraisal of the literature reviewed. The identification of the model's key dimensions, addressed by each of the selected articles, provides a measure of convergence of thought that was previously unmeasured.

As indicated in Table 5, very few articles addressed only a single dimension; generally these pertained to the economic issues of health technology or the role of technology assessment in decision making. The large majority of the reviewed articles examined ethical concerns regarding health care technology most frequently discussed as questions of equity. Related closely were issues of the social impact of health technologies and, therefore, social costs. In particular, questions regarding experimental, expensive, or newly introduced technologies were raised, especially in terms of the need to understand how these affect social relations, current and future, for the patient and family or friends as well as the health care providers. The emotional costs of new choices, paradoxical effects on individuals and stakeholder groups, and the often false sense of freedom that arises were postulated to be at least as important as financial costs. The literature also indicates that the burden of illness is ultimately shared by society at large; while one individual may be the recipient of a public good — in the form of a technological intervention paid for through universal health insurance — other individuals have to forgo other public goods in health care or other public services.

There is also appreciable convergence in the literature on the political aspects of resource allocation. The evidence indicates that although it can establish the safety, efficacy, and effectiveness of technologies, scientific knowledge does not provide the answer to "how much technology and for whom?" These types of decisions should be made by officials elected to represent the public interest, accountable to a legislative body. On the one hand, it is generally held that public policy makers are responsible for the public interest. On the other hand, it is often assumed (both by providers and patients) that health professionals, as providers, are responsible only to the individuals under their care. There is growing literature, however, to indicate that providers should bear some public responsibility as stewards of the common wealth.

Although the field of technology assessment is a relatively new one, fraught with the usual problems of multidisciplinary work, the research evidence indicates that the usefulness of scientific evidence is limited if

produced in a way that is divorced from the decision-making processes. The value of integrating technology assessment research with public policy was recognized more than a decade ago (Bozeman and Rossini 1979). It was suggested that the research process should include the interplay of values, making it part of the bureaucratic-political environment. The importance of linking research findings to clinical, administrative, or policy decisions is clearly a point of convergence in the present findings. Regardless of disciplinary perspective, researchers agree that political considerations must be an important dimension of technology assessment. Increasing the involvement of the decision makers in the research process would increase their commitment to use the research evidence (Banta and Andreasen 1990; Drummond 1990).

Literature is slowly emerging that evaluates research evidence, whether the evaluation is economic or clinical (Laupacis 1992; Larson 1989). As the integration of technology assessment and decision making becomes better coordinated, attention should be paid to eliminating the structural barriers to such integration, usually through the clarification of long-standing ambiguities regarding decision-making authority. As well, the resolution of disputes between government and medicine, or between government and hospitals, over who decides what issues would clarify who should be the target audience for the information generated through technology assessment (Lomas 1990).

It is reasonable to conclude that health care systems are grounded in societal norms and propelled by culturally defined value systems that are not immutable over time. Thus, changing values in Canadian society (as well as in the rest of the Western world) have altered the traditional relationships between government, medical practitioner, and health care consumer, with a consequent shift in their respective authority to manage the system. The public is now less likely to wish the medical practitioner to have paternalistic attributes, and at the same time is also less likely to unquestioningly transfer these attributes to public officials. Because views of the human condition, concepts of health and disease, approaches to medical practice, and notions of distributive justice are culturally defined, incorporating these underlying paradigms in research may shed better light on outcomes of care than simply studying the technical capacity of the health care system.

Analysis of the data (see Table 5) revealed that only 5% of the studies were empirically based. Much more work needs to be undertaken on how decisions regarding public policy ought to be made to best serve the public interest.

Concluding Remarks

The purpose of the proposed decision framework (see Table 1) is the creation of a clear, precise, manageable, and replicable process designed to

generate information about the consequences of the various decision options. Models are fundamental to policy analysis. Although they may not predict consequences with the same assurance as the best scientific models, policy models tell us what the possibilities are, based on various assumptions about the factors of concern. Decisions are often made intuitively, without explicit models. However, in that case, a tacit model or an unconsciously calculated decision is being developed. Faced with a phenomenon that is too complex and too expensive to study directly, a natural inclination is to study a model that resembles the phenomenon framework of interest in its essential features, but is more manageable, less expensive, and easier to study.

It is possible to test the predictions based on a model and determine the correctness and relevance of these predictions for real-world decisions. The present proposed conceptual model provided broad barometers within which a literature review was conducted. A critical appraisal of the literature provided an examination of the quality and volume of the evidence pertaining to health technology decisions. Evidence pertaining to the attributes of health care technologies was not investigated. This literature review was undertaken primarily to establish the feasibility of the model's empirical application.

The literature reviewed for this project clearly indicated that the dimensions of the proposed framework were the appropriate ones to include in a health technology decision model. Although these factors were not always grouped indentically to the model, singly or in multiples the same factors appeared in most of the literature examined. In addition, the evidence from the literature review indicated that the decision-making process, as described by the referenced studies, is receptive to systematic inputs of information that enhance the potential for better decisions. Several of the articles reviewed proposed decision models with similar, but usually less comprehensive, characteristics (see, for example, Balk 1990; Deber and Goel 1990; Eddy 1991c; Hadorn 1991a; Kaplan and Anderson 1988; Murphy and Matchar 1990).

A second general comment about the findings pertains to the technical feasibility of developing the mathematical model based on the suggested conceptual one. The degree of difficulty in developing quantitative measures for each of the model dimensions will vary appreciably from one dimension to the next, but the task is not an impossible one. Economic and epidemiologic measures are easier to compile from already existing ones, compared to developing measures for ethical and social concerns; quantification of the political milieu may prove an even more challenging exercise. However, these methodological hurdles do not appear to be insurmountable in light of the evidence on the importance of using norms of utility as well as equity in making health technology decisions.

Appendix 1

Search Strategies and Results

1. ABI/INFORM
2. US Political Science Documents
3. Economic Literature Index
4. Sociological Abstracts
5. Medline
6. Health Planning and Administration (Health Data Base)
7. Biobusiness
8. MATHSCI
9. Health Periodicals Data Base
10. FRANCIS

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
ABI/INFORM 1986 - November 1991	1	decision making models	497
		decision theory	433
		decision making models 'or' decision theory	850
	2	strategic planning	4 660
		technological planning	184
		strategic planning 'or' technological planning	4 817
	3	public policy	1 568
		social policy	680
		public policy 'or' social policy	2 224
	4	decision	8 598
		policy	15 577
		decision 'or' policy	23 700
	5	searches 1 'and' 2 'and' 3 'and' 4 = decision	28 214

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	6	searches 1 'and' 2 'and' 3 'and' 4 = decision	1
	7	health	7 877
		medical devices	266
		hospitals	4 238
		health 'or' medical devices 'or' hospitals = health care	10 921
	8	searches 5 'and' 7 = decisions related to health care	1 502
	9	epidemics	37
		diseases	427
		epidemics 'or' diseases	440
	10	illnesses	228
		population	639
		illnesses 'or' population	867
	11	incidence	12
		prevalence	0
		incidence 'or' prevalence	12
	12	population	639
		impact	8 145
		population 'and' impact	64
	13	demography	1 197
	14	searches 12 'or' 13	1 249
	15	searches 9 'or' 10 'or' 11 'or' 14	2 335
	16	lifetables	0
		statistical data	15 446
	17	searches 15 'or' 16 = population health/population impact	17 303

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	18	searches 8 'and' 17 = decisions related to health care and population health/population impact	149
	19	economics	22 370
		costs	11 162
		expenditures	5 017
		economics 'or' costs 'or' expenditures = economics	35 499
	20	searches 8 'and' 19 = decisions related to health care and economics	61
	21	research	7 179
		R & D	3 659
		research 'or' R & D	10 534
	22	technology	5 007
		technology transfer	517
		technology 'or' technology transfer	5 007
	23	appropriate technology	7
		high technology	1 140
		appropriate technology 'or' high technology	1 147
	24	technology diffusion	0
	25	searches 21 'or' 22 'or' 23 = technology	14 649
	26	searches 8 'or' 25 = decisions related to health care and technology	48
	27	justice	175
		law	16 665
		justice 'or' law	16 745
	28	government	5 400

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	29	searches 27 'or' 28 = law	21 534
	30	searches 8 'and' 29 = decisions related to health care and law	200
	31	politics	700
		political risk	320
		politics 'or' political risk	1 005
	32	power	2 217
	33	searches 31 'or' 32	3 183
	34	public opinion surveys	161
		polls	63
		public opinion surveys 'or' polls	196
	35	advocacy	44
		consumerism	115
		advocacy 'or' consumerism	154
	36	searches 34 'or' 35	349
	37	searches 33 'or' 36 = politics	3 525
	38	searches 8 'and' 37 = decisions related to health care and politics	29
	39	ethics	1 684
		social impact	131
		ethics 'or' social impact	1 810
	40	quality of life	115
	41	searches 39 'or' 40 = ethics	1 922
	42	searches 8 'and' 41 = decisions related to health care and ethics	28

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
US Political Science Documents (1975-1991)	1	administrative policy making/DE	76
	2	committee decision making/DE	50
	3	administrative policy making/DE 'or' decision maker perception/DE	126
	4	community decision making/DE	118
	5	decision maker perception/DE	375
	6	community decision making/DE 'or' decision maker perception/DE	493
	7	decision making analysis/DE	758
	8	decision making theory/DE	374
	9	decision making analysis/DE 'or' decision making theory/DE	949
	10	decision making process/DE	760
	11	judicial decision making/DE	289
	12	decision making process/DE 'or' judicial decision making/DE	1 045
	13	legislative decision making/DE	139
	14	planning process/DE	201

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	15	legislative decision making/DE 'or' planning process/DE	339
	16	policy analysis/DE	716
	17	policy development/DE	518
	18	policy evaluation/DE	2 611
	19	policy analysis/DE 'or' policy development/DE 'or' policy evaluation/DE	3 462
	20	policy evaluation process/DE	0
	21	public choice analysis/DE	276
	22	policy evaluation process/DE 'or' public choice analysis/DE	276
	23	public policy analysis/DE	1 573
	24	public policy planning	284
	25	public policy analysis/DE 'or' public policy planning	1 678
	26	science information policy/DE	14
	27	policy evaluation research	294
	28	science information policy/DE 'or' policy evaluation research	308
	29	3 'or' 6 'or' 9 'or' 12 'or' 15 'or' 19 'or' 22 'or' 25	7 093
	30	health administration/DE	89
	31	health care agency/DE	38
	32	health care agency/DE	38
	33	health administration/DE 'or' health care agency/DE 'or' health care agency/DE	115

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	34	health care institution/DE	38
	35	health care policy/DE	175
	36	health care rights/DE	91
	37	health care institution/DE 'or' health care agency/DE 'or' health care rights/DE	267
	38	health care system/DE	298
	39	medical care system/DE	142
	40	medical education/DE	50
	41	health care system/DE 'or' medical care system/DE 'or' medical education/DE	413
	42	national health insurance/DE	51
	43	public health policy/DE	269
	44	socialized medicine system/DE	3
	45	national health insurance/DE 'or' public health policy/DE 'or' socialized medicine system/DE	307
Economic Literature Index (1969 - December 1991)	1	decision () making	1 424
	2	search 1 'and' health () care	3
	3	search 1 'and' assess? 'and' technolog?	3
	4	search 1 'and' medic?	21
	5	2 'or' 3 'or' 4	24
	6	search 1 'and' model?	379

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	7	search 6 'and' (cost? 'or' fund? 'or' spend? 'or' expend? 'or' financ?)	84
	8	search 6 'and' (rationaliz? 'or' equitable 'or' inequitable)	2
	9	7 'not' 8	84
	10	search 1/TI, DE	1 046
		search 10 'and' model? - search 10	1 046
		search 10 'and' model? - model?	38 202
	11	search 10 'and' model?	229
		11	229
		7	84
	12	11 'and' 7	23
Sociological Abstracts (1963 - December 1991)	1	decision () making	8 006
	2	search 1 'and' feminis?	199
	3	search 1 'and' female	300
	4	2 'or' 3	408
	5	search 4 'and' reproductive 'and' technolog?	2
	7	feminist/ID	1 133
	8	feminist/DE	597
	9	7 'or' 8	1 402
	11	policy/DE 'and' decision () making/DE	201
	12	social () policy/DE	1 096
	13	search 12 'and' decision () making/DE	42

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	14	13 'not' 5	42
	15	9 'and' 11	0
	16	government?/DE	3 588
	17	search 1 'and' government?/DE	353
	18	technology	22 027
	19	search 17 'and' technology	23
	20	technolog?	25 261
	21	search 17 'and' technology	31
	22	21 'and' 9	0
	23	politic?	53 339
	24	search 1 'and' politic?	1 944
	25	feminis?	11 995
	26	search 24 'and' feminis?	38
	27	26 'not' 5	38
		assess (search limited to 64-85)	3 651
		technolog?	25 261
	28	assess (3N) technolog?	16
		search 28 'and' decision - search 28	16
		search 28 'and' decision - decision?	14 644
	29	search 28 'and' decision?	2
MEDLINE (1987 - January 1992)	1	decision making (all)	2 302
		decision making (focus)	893
	2	decision making, organizational (all)	319
		decision making, organization (focus)	145

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	3	decision theory (all)	101
		decision theory (focus)	44
	4	decision support techniques (all)	424
		decision support techniques (focus)	275
	5	searches 1 'or' 2 'or' 3 'or' 4 = decision	1 334
	6	health policy (all)	3 234
		health policy (focus)	1 884
	7	public policy (all)	860
		public policy (focus)	458
	8	searches 6 'or' 7 = policy	2 338
	9	searches 5 'and' 8 = decisions related to policy	14
	10	delivery of health care	3 089
	11	searches 5 'and' 10	20
	12	searches 8 'and' 10 (search limited to 1991-92)	13
	13	health expenditures	340
	14	searches 5 'and' 13	1
	15	searches 8 'and' 13	10
	16	health	1 126
	17	searches 5 'and' 16	3
	18	searches 8 'and' 16	13
	19	health care rationing	416
	20	searches 5 'and' 19	16
	21	searches 8 'and' 19	27
	22	health facilities	722
	23	searches 5 'and' 22	7
	24	searches 8 'and' 22	12

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	25	health planning	924
	26	searches 5 'and' 25	4
	27	searches 8 'and' 25 (search limited to 1990-92)	13
	28	health priorities	406
	29	searches 5 'and' 28	3
	30	searches 8 'and' 28 (search limited to 1990-92)	8
	31	health resources	653
	32	searches 5 'and' 31	12
	33	searches 8 'and' 31 (search limited to 1990-92)	7
	34	health services	1 702
	35	searches 5 'and' 34	2
	36	searches 8 'and' 34 (search limited to 1990-92)	24
	37	health services research	1 670
	38	searches 5 'and' 37	14
	39	searches 8 'and' 37 (search limited to 1990-92)	21
	40	health status indicators	755
	41	searches 5 'and' 40	4
	42	searches 8 'and' 40	10
	43	health surveys	1 473
	44	searches 5 'and' 43	4
	45	searches 8 'and' 43	12
	46	technology assessment, biomedical	473
	47	searches 5 'and' 46	14
	48	searches 8 'and' 46	11

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	49	ethics, medical	4 411
	50	searches 5 'and' 49	86
	51	searches 8 'and' 49	63
	52	population surveillance	1 554
	53	searches 5 'and' 52	0
	54	searches 8 'and' 52	4
	55	technology, medical	672
	56	searches 5 'and' 55	8
	57	searches 8 'and' 55	6
	58	technology, pharmaceutical	298
	59	searches 5 'and' 58	0
	60	searches 8 'and' 58	4
	61	technology, radiologic	755
	62	searches 5 'and' 61	0
	63	searches 8 'and' 61	3
	64	United States Office of Technology Assessment	21
	65	searches 5 'and' 64	0
	66	searches 8 'and' 64	4
	67	cost benefit analysis	2 469
	68	searches 5 'and' 67	56
	69	searches 8 'and' 67	34
Health Planning and Administration (1975 - January 1992)*	1	decision making (all) decision making (focus)	6 693 2 073

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	2	decision making, organization (all)	826
		decision making, organizational (focus)	423
	3	decision theory (all)	153
		decision theory (focus)	61
	4	decision support techniques (all)	250
		decision support techniques (focus)	149
	5	searches 1 'or' 2 'or' 3 'or' 4 = decision (limited to articles with 'focus')	2 691
	6	health policy (all)	7 721
		health policy (focus)	4 835
	7	public policy (all)	2 854
		public policy (focus)	4 835
	8	searches 6 'or' 7 = policy (limited to articles with 'focus')	6 434
	9	searches 5 'and' 8	33
	10	searches 5 'or' 8	9 092
	11	delivery of health care	12 209
	12	searches 11 'and' 10	599 (all)
		searches 11 'and' 10	33 (search limited to 87-92; MEDLINE eliminated)
	13	health expenditures	2 769
	14	searches 13 'and' 10	193 (all)
		searches 13 'and' 10	54 (search limited to 87-92; MEDLINE eliminated)

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	15	health	3 483
	16	searches 15 'and' 10	66 (all)
		searches 15 'and' 10	14 (search limited to 87-92; MEDLINE eliminated)
	17	health care rationing	552
	18	searches 17 'and' 10	58 (all)
		searches 17 'and' 10	11 (search limited to 87-92; MEDLINE eliminated)
	19	health facilities	4 283
	20	searches 19 'and' 10	60 (all)
		searches 19 'and' 10	11 (search limited to 87-92; MEDLINE eliminated)
	21	health planning	4 718
	22	searches 21 'and' 10	268 (all)
		searches 20 'and' 10	28 (search limited to 87-92; MEDLINE eliminated)
	23	health priorities	962
	24	searches 23 'and' 10	101
		searches 23 'and' 10	16 (search limited to 87-92; MEDLINE eliminated)
	25	health resources	2 340

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	26	searches 25 'and' 10 searches 25 'and' 10	214 (all) 25 (search limited to 87-92; MEDLINE eliminated)
	27	health services	5 777
	28	searches 27 'and' 10 searches 27 'and' 10	196 (all) 4 (search limited to 87-92; MEDLINE eliminated)
	29	health services research	4 273
	30	searches 29 'and' 10 searches 29 'and' 10	198 (all) 27 (search limited to 87-92; MEDLINE eliminated)
	31	health status indicators	1 591
	32	searches 31 'and' 10 searches 31 'and' 10	38 (all) 4 (search limited to 87-92; MEDLINE eliminated)
	33	health surveys	3 949
	34	searches 33 'and' 10 searches 33 'and' 10	38 (all) 4 (search limited to 87-92; MEDLINE eliminated)
	35	technology assessment, biomedical	1 406

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	36	searches 35 'and' 10	92 (all)
		searches 35 'and' 10	34 (search limited to 87-92; MEDLINE eliminated)
	37	ethics, medical	8 045 (all)
	38	searches 37 'and' 10	278 (all)
		searches 37 'and' 10	25 (search limited to 87-92; MEDLINE eliminated)
	39	population surveillance	1 314
	40	searches 39 'and' 10	8 (all)
		searches 39 'and' 10	0 (eliminated MEDLINE)
	41	technology, medical	2 218
	42	searches 41 'and' 10	84 (all)
		searches 41 'and' 10	3 (search limited to 87-92; MEDLINE eliminated)
	43	technology, pharmaceutical	211
	44	searches 43 'and' 10	8 (all)
		searches 43 'and' 10	2 (eliminated MEDLINE)
	45	technology, radiologic	1 215
	46	searches 45 'and' 10	4 (all)
		searches 45 'and' 10	1 (eliminated MEDLINE)
	47	United States Office of Technology Assessment	32

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	48	searches 47 'and' 10	4 (all)
		searches 47 'and' 10	0 (eliminated MEDLINE)
	49	cost benefit analysis	7 007
	50	searches 49 'and' 10	249 (all)
		searches 49 'and' 10	15 (search limited to 87-92; MEDLINE eliminated)

* Overlap between Health Planning and Administration and MEDLINE has been eliminated in the Health Planning and Administration Search.

Biobusiness	1	equitable	43
		decision/TI, DE	2 440
		making/TI, DE	2 118
	2	decision () making/TI, DE	713
		1 'and' 2 - 1	43
		1 'and' 2 - 2	713
	3	1 'and' 2	1
		search 2 'and' (legislate? 'or' government? 'or' rationalize 'or' inequitable 'or' spending 'or' financ?) - search 2	713
	4	legislat?	50 086
	5	government?	25 650
	6	rationalize	22
	9	spending	1 850
	10	financ?	4 743

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	11	search 2 'and' (legislat? 'or' government? 'or' rationalize 'or' inequitable 'or' spending 'or' financ?)	375
		search 2 'and' expend - search 2	713
	12	expend?	644
	13	search 2 'and' expend?	2
		13 'or' 11 - 13	2
		13 'or' 11 - 11	375
	14	13 'or' 11	375
		search 14 'and' health () care - search 14	375
	15	health	33 929
	16	care	9 083
	17	health (W) care	4 094
	18	search 14 'and' health () care	6
		search 14 'and' drugs - search 14	375
	19	drugs	6 324
	20	search 14 'and' drugs	5
		search 14 'and' technolog? - search 14	375
	21	technolog?	22 633
	22	search 14 'and' technolog?	28
		search 14 'and' health () policy - search 14	375
	23	health	33 929
	24	policy	8 246
	25	health (W) policy	51

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
	26	search 14 'and' health () policy	0
		search 14 'and' health (3N) (policy 'or' policies 'or' projects) - search 14	375
	27	health	33 929
	28	policy	8 246
	29	policies	1 403
	30	projects	1 021
	31	health (3N) (policy 'or' policies 'or' projects)	95
	32	search 14 'and' health (3N) (policy 'or' policies 'or' projects)	0
		18 'or' 20 - 18	6
		18 'or' 20 - 20	5
	33	18 or 20	11
MATHSCI	1	decision () making/TI, DE	1 336
	2	search 1 'and' model?/TI, DE	259
	3	search 2 'and' (cost? or fund? or spending or expend? or financ?)	13
	4	search 2 'and' health	1
	5	search 2 'and' medi	11
	6	search 2 'and' medic?	9
	7	search 2 'and' fund? 'and' projects	1
	8	search 2 'and' assess? 'and' technology	0
	9	assess? (F) technology	106
	10	search 9 'and' decision?	18

DATA BASE	SEARCH NUMBER	SEARCH WORD(S)	NO. OF ARTICLES
Health Periodicals	1	decision adj making.de.	707
	2	reproduct$	3 046
	3	1 'and' 2	10
	4	technolog$.TI,DE.	4 685
	5	1 'and' 4	13
	6	3 'or' 5	23
	7	1 'and' investment	1
	8	1 'and' feminis$	3
	9	technology adj assessment.de.	171
	10	1 'and' 9	1
	11	9 'and' decision$.TI, DE.	3
FRANCIS	1	decision W making	1 383
	2	decision/TI	2 214
	3	decision/TI	3 379
	4	health 'or' medicine	31 820
	5	health 'or' medical	26 488
	6	decision (W) making 'and' health	27
	7	decision (W) making 'and' medical	24
	8	8 'not' 7	14 229

Notes

1. A search on CUADRA On-Line Data-Base was undertaken to determine which data bases would best capture the feminist literature. The search indicated that Sociological Abstracts was the most appropriate. For a description of CUADRA, see section entitled "North American Data Bases."

2. On-line data-base searching employs Boolean logic, a method of logic developed by the mathematician and logician George Boole. Boolean operators combine sets or terms in various relationships. The major logical operators are 'and,' 'or,' and 'not.' 'And' is used to combine concepts. It will retrieve records containing both terms or sets in a combination. 'Or' is used to search on all or any concepts. It will retrieve records containing all or any terms in the statement. 'Not' is used to exclude information.

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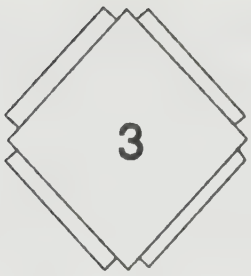
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Infertility Treatment: From Cookery to Science — The Epidemiology of Randomized Controlled Trials

Patrick Vandekerckhove, Patricia A. O'Donovan, Richard J. Lilford, and T.W. Harada



Executive Summary

For many couples who have difficulty reproducing, infertility treatment may be administered to the male or female partner (or both). The diagnosis may be explicit, pertaining to one given explanation or specific to one partner, or it may be unexplained male or female infertility. Couples may have deep-seated motivations for bearing children, and the desire to assist medically is strong; however, an objective assessment of treatments and effects must be carried out.

Random assignment of couples to receive treatment or not to receive treatment is required to assess the many treatments that could be tried, because some couples might conceive in time if no treatment were given, and experimental bias (in several forms) is difficult to avoid. To assess the treatments given from 1966 to 1990, MEDLINE was used and a search of 41 journals was carried out. Detailed data were entered into an ongoing, extensive data base that contains information about the location and source of each study, experimental parameters, outcome measures, outcomes, and treatment facts. Results and literature reviews

This paper was completed for the Royal Commission on New Reproductive Technologies in June 1992.

are reported separately for men and women in this paper, and details concerning further analyses are presented in *Treatment of Male Infertility: Is it Effective? A Review and Meta-Analyses of Published Randomized Controlled Trials*, also published by this Commission.

Methodological weakness was apparent from the literature review, though recent increases in the number of randomized controlled studies were apparent. Research should be designed with experimental control and statistical power in mind, and the authors recommend multicentred, cooperative research.

Introduction

About 60% of all patients attending infertility clinics will eventually conceive (Katayama et al. 1979; Philipp 1987). Many would have conceived anyway (Lilford and Dalton 1987); for some, medical intervention might reduce fertility (Vere and Joyce 1979; McBain et al. 1990).

For some treatments, pregnancy can be taken as virtual proof of effectiveness; pregnancy by *in vitro* fertilization (IVF) following bilateral salpingectomy or by donor insemination in azoospermia would be examples. More often, couples are subfertile rather than sterile, and it is tempting to give undeserved credit to medical interventions when pregnancies occur. Pregnancy rates, therefore, should be compared between study patients and controls, and, as in other branches of medicine, control patient groups should be generated at random to avoid selection bias.

In 1979, Dr. A. Cochrane chose obstetrics and gynaecology as the speciality most deserving of the wooden spoon for implementing unproven therapies (Cochrane 1979), but this slur was removed with the publication of *Effective Care in Pregnancy and Childbirth* (Cochrane 1989). It is the present authors' impression that randomized methodology has been underutilized in infertility studies, and, if the wooden spoon is to be reallocated, it might well be awarded to clinicians in this speciality.

Individual trials often fail to provide unequivocal answers to clinical questions, even when designed and executed appropriately, because of limited sample size and power. However, the science of "meta-analysis" has emerged as a useful tool to address this problem. This quantitative approach to summarizing evidence has generated significant interest in the medical literature. The methodology of meta-analysis is similar to that of other scientific research: a specific question is posed and refined, information is identified and extracted in an unbiased way based on predetermined inclusion criteria, and, finally, where appropriate, data are combined using formal statistical techniques to allow valid conclusions to be drawn.

The present authors have reviewed the literature to evaluate the quantity and quality of randomized trials in the treatment of subfertility. This work has now become part of an international collaborative effort with

the McMaster University Department of Obstetrics and Gynaecology, Hamilton, Ontario (Canada). Detailed overviews and meta-analyses of selected topics are to be carried out with our collaborators. A register of infertility trials is to be maintained and ultimately merged with a more extensive data base, *Effective Care in Gynaecology*, edited by G.J. Jarvis, J.O. Drife, and R.J. Lilford (commissioned by Oxford University Press).

Materials and Methods

A computerized MEDLINE search was conducted to identify all registered articles in all languages, published before 1991, concerned with human infertility. The searches were carried out under the following keywords for titles and abstracts: infertility, human, infertility male, infertility female, clinical trials, random allocation, comparative study, double-blind method. All articles listed as trials were selected. All trials ascertained in this way (not only those coded as randomized trials) were reviewed and classified as to whether they were randomized and according to whether they dealt with male or female infertility or both.

To reduce the risk that a significant number of studies were missed through the MEDLINE search, all articles in 41 journals (Appendix 1) thought likely to yield the highest number of studies were reviewed manually. The journals were selected on the basis of discussions with colleagues, personal knowledge, and results of the initial MEDLINE search. The hand search included journals published from 1966 onward, so that the whole period covered by MEDLINE (1966-1990) would be examined. References at the end of relevant papers and those mentioned in review articles were checked.

A trial was eligible for inclusion if it dealt with any aspect of the treatment of infertility and contained a control group created by a randomization procedure. All identified eligible trials were obtained, reviewed, and analyzed for inclusion criteria. If sufficient details could not be obtained via the British Library, editors of small-circulation journals (mainly from Eastern Europe and South America) were contacted by mail.

Data concerning each trial were entered into a computer data base (dBASE IV). The method by which each trial was identified (i.e., MEDLINE, hand search, printed reference, or verbal reference) was also noted. All trials were classified as to whether they dealt with the treatment of male or female infertility, the specific topic investigated, the country from which the report emanated, and the source of any funding. Trials were subclassified further according to several "quality" criteria. Whether or not pregnancy was a measured outcome was noted and, if so, how it was diagnosed (biochemical, gestational sac or fetal heart on ultrasound, delivery, live child, or not specified). The latter consideration is particularly relevant in the trials dealing with modern assisted-conception techniques. Pregnancy

rates were classified on a per cycle or per patient basis; in the latter case, the completeness and duration of follow-up were noted. The sample size and whether or not a power calculation was performed were noted. Trials were classified as multi- or single-centre studies and according to the method of randomization, i.e., truly randomized, pseudo-randomized, or not specified. Studies were also classified according to the use of single-phase or crossover designs. The "impact factor" of each journal was derived from the *Science Citation Index*, which gives a figure for the relative frequency with which the journal's average article has been cited. The odds ratios of results of individual studies and their 95% confidence intervals were calculated following the method of Morris and Gardner (1988). Quantitative meta-analysis was performed using the Mantel-Haenszel equation, provided that sufficient data were given.

Results

The MEDLINE search identified 80 trials. Twenty-three of the trials involving males were pregnancy trials, as were 42 of the trials involving females. In total, only 46 of the trials involving infertility treatment were found to be truly randomized controlled trials. Nine trials identified by MEDLINE were pseudo-randomized, and in 25 trials the method of randomization was not specified. Another trial registered as a randomized trial in infertility treatment by MEDLINE was indeed randomized, but did not deal with infertility treatment at all (Goldman et al. 1969).

Four hundred and twenty-one (144 male and 277 female) additional randomized trials were discovered during the journal review. Sixteen of the publications were single articles containing results from two trials on a similar subject and were regarded as two separate trials. Seven other studies were found to be a combination of a trial involving both males and females — as each of these studies could have been reported as two separate studies, they were regarded as such for the present analysis (Buvat et al. 1987; Leeton et al. 1987; Melis et al. 1987; Leong et al. 1988; Friedman et al. 1989; te Velde et al. 1989; Martinez et al. 1990). The study by Buvat et al. (1987), which investigated anti-estrogens as a treatment for female and male infertility, used a randomized design for the women studied but not for the men. Six randomized trials were so highly regarded by their authors that identical data were published twice (Friberg and Gemzell 1973, 1977; van Dijk et al. 1979a, 1979b; Frydman et al. 1988a, 1988b; Telimaa 1988; Kauppila et al. 1989; Van Steirteghem et al. 1988 and Smitz et al. 1988) or even three times (Henzl et al. 1988, Henzl 1989, and Henzl and Kwei 1990), with some of the patients of the last trial reported again as part of another study (Burry et al. 1989). Another twice-published trial appeared to be a genuine mistake, with the same article appearing in the same journal with an interval of two issues (Colpi et al.

1986a, 1986b). All of these sets of trials were counted as one trial, the first published paper being included.

In some cases, authors republish the same trial but with additional information, such as a larger number of variables or other outcome variables (Thomas and Cooke 1987b; Cooke and Thomas 1989; Dodson et al. 1989; Bachus et al. 1990; Fedele et al. 1989b, 1990; Valimaki et al. 1989 and Ylikorkala et al. 1990) or an expansion of the original sample (Dodson et al. 1987, 1989). Again, these were registered as a single trial. Factorial design trials, in which the same group of patients is randomized more than once, were registered as a single trial, but the different interventions were analyzed separately.

In this way, 174 male and 327 female trials were identified. Seventy-two male and 215 female trials had pregnancy as an outcome.

Appendix 2 shows randomized trials in which pregnancy was a measured outcome and pregnancy rates were expressed on a per patient basis for male (Appendix 2A) and female (Appendix 2B) infertility. The number of patients in each trial, method of randomization, and odds ratios with 95% confidence intervals are shown for each trial. Knowledge of the duration of follow-up of the patients is essential for interpreting pregnancy results, but was not given in two trials (Swolin 1967; Noble and Letchworth 1980).

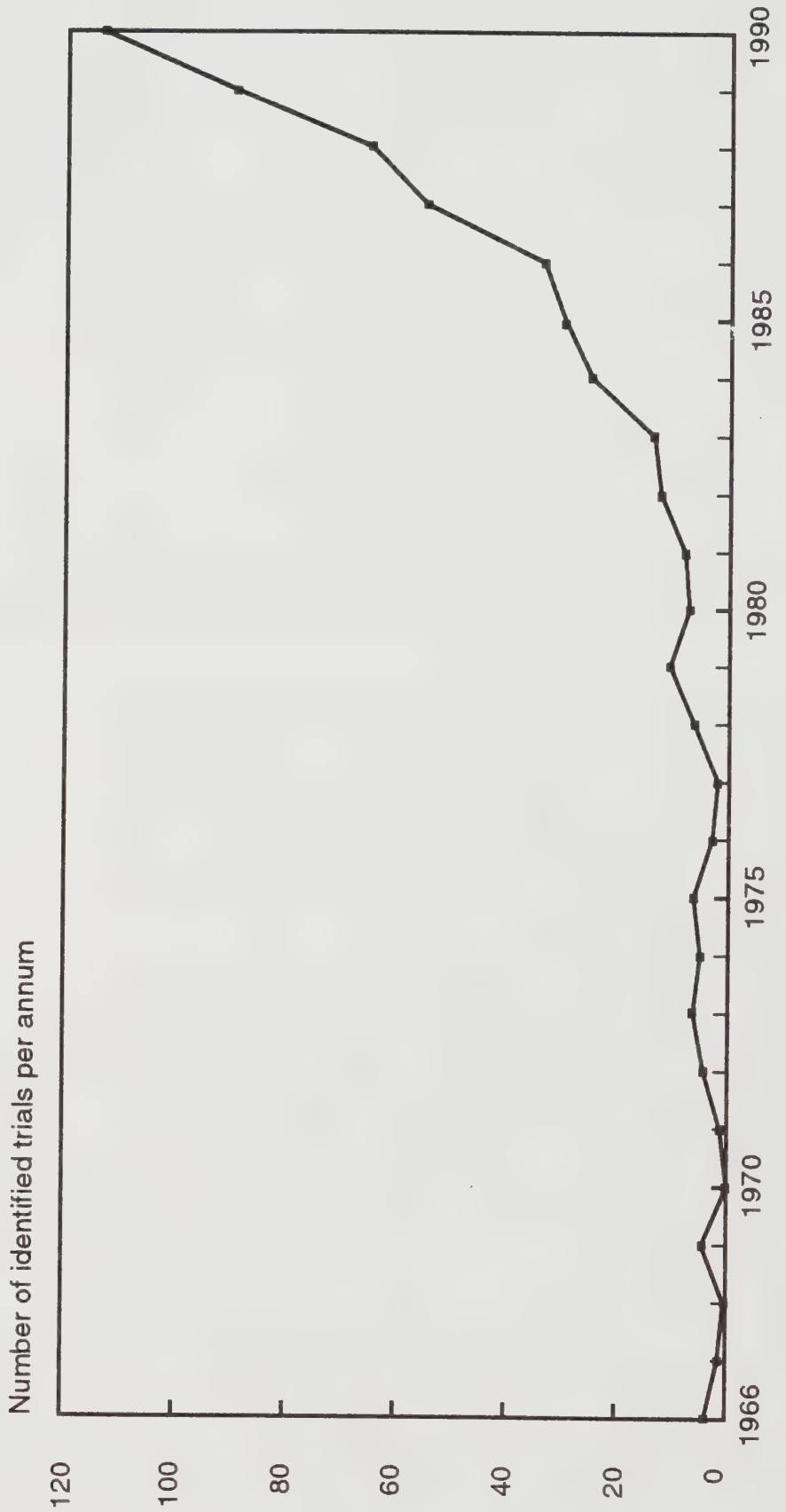
Appendix 3 shows randomized trials in which pregnancy is expressed on a per cycle basis for male (Appendix 3A) and female (Appendix 3B) infertility. Authors sometimes presented their results according to the treatment actually given, rather than the originally assigned groups (e.g., Leong et al. 1988). When this happened, the typical odds ratio and confidence limits were recalculated according to the original groups if the necessary data were included in the text.

Remaining trials with pregnancy as an outcome that contained insufficient data for the calculation of an unbiased odds ratio, had major trial design errors, used crossover design with insufficient data to analyze the results before the crossing over of treatments, or contained multiple comparison groups are listed in Appendices 4A and 4B.

Trials with outcomes other than pregnancy, and those in which gametes (rather than patients) were randomized to different *in vitro* handling procedures, are classified separately and are available from the authors upon request.

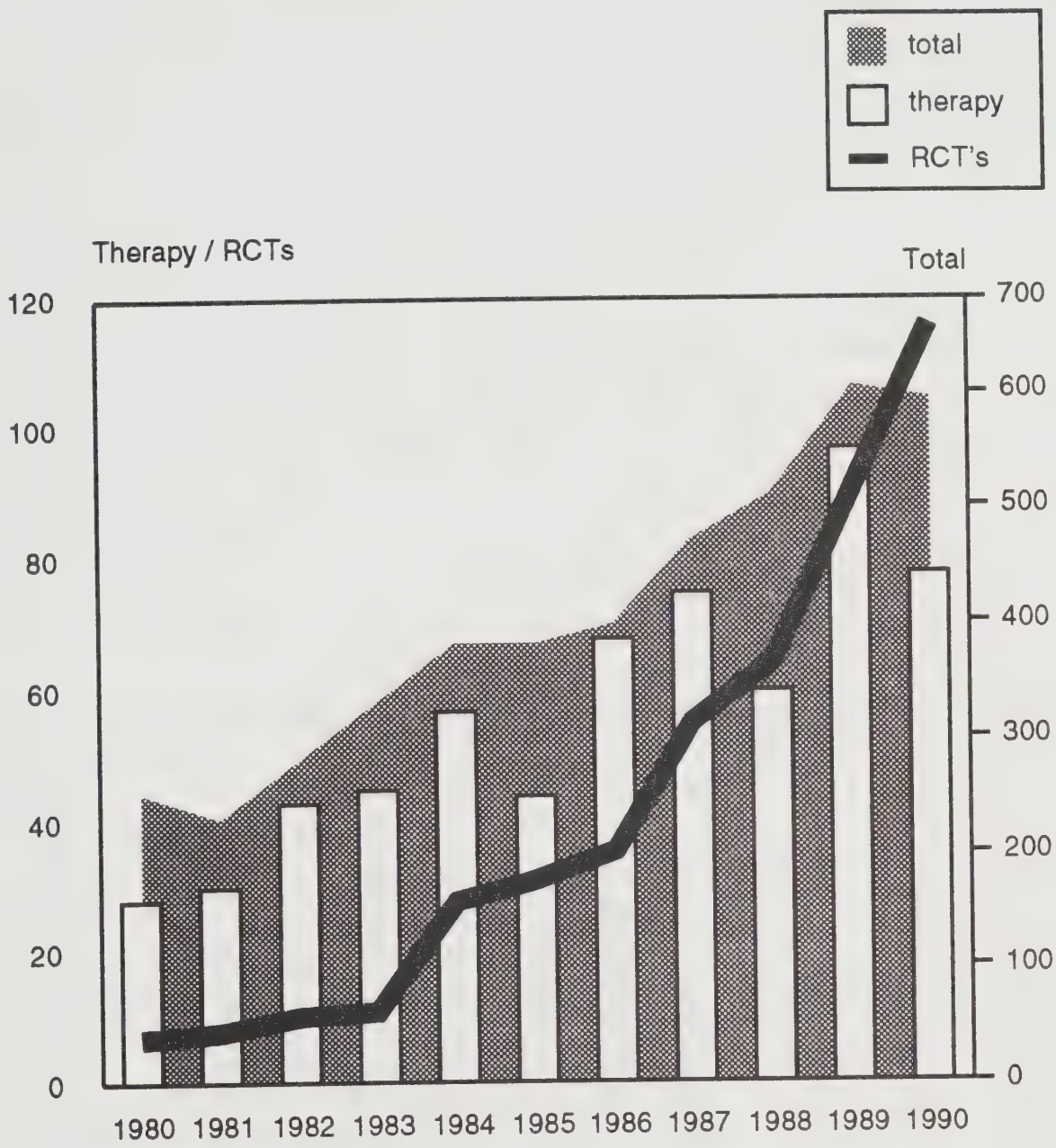
The number of randomized infertility treatment trials, based on the year of publication, has increased over the last few years (Figure 1). The total number of infertility publications per annum has also increased, but at a slower rate, so that the proportion of studies using randomized methodology has risen substantially (Figure 2).

Figure 1. Randomized Controlled Infertility Treatment Trials per Annum



Note: The exponential rise in identified randomized infertility treatment trials 1966-1990.

Figure 2. Infertility and Infertility Therapy Publications

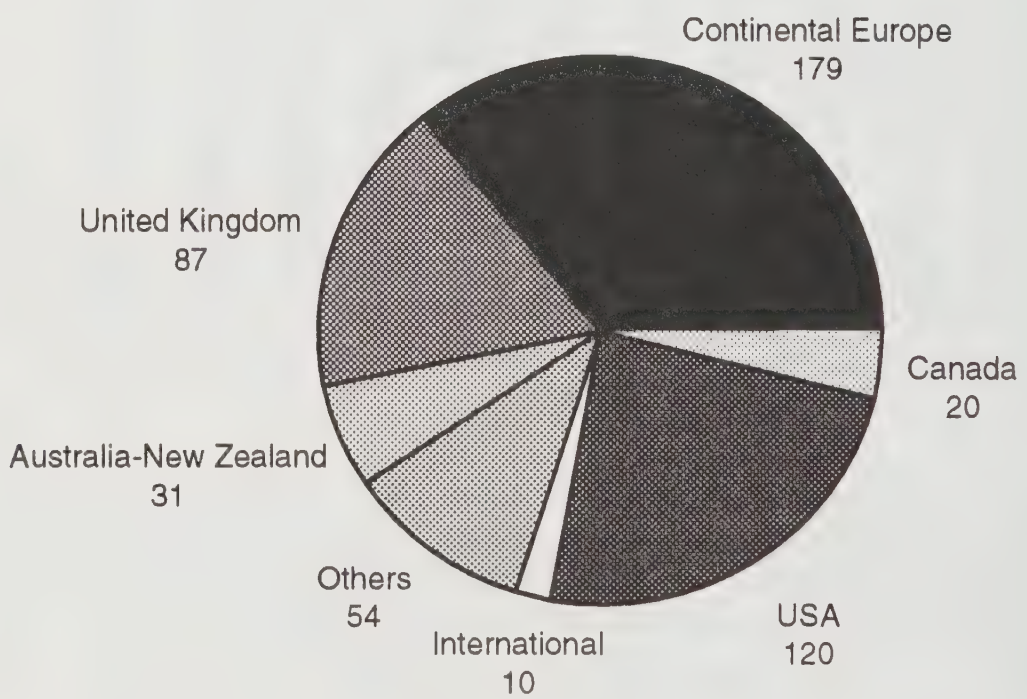


Note: Total number of infertility and infertility therapy publications per annum (both identified through Medline) compared with the number of randomized controlled trials (RCT's) in fertility treatment. The increase in randomized controlled trials is not only absolute but also proportionate.

Examination of the contribution of different countries to randomized trials in infertility treatment shows continental Europe producing the largest number, followed by the United States and the United Kingdom (Figure 3). Because of the search strategy used, these figures may be biased in favour of English-speaking countries; therefore, collaborators in other non-English-speaking countries were sought. Dr. T.W. Harada, Tottori University School of Medicine, Japan, reviewed *Acta Obstetrica et Gynaecologica Japonica* for the period 1975 to 1990 and "could not find any study in which the author clearly stated that this is a randomized study."

The 41 hand-searched journals reviewed in this study and their impact factors are listed along with the number of randomized trials identified in each journal in Appendix 1. *Fertility and Sterility* published the largest number of randomized controlled trials (145), followed by *Human Reproduction* (58), the *Journal of In Vitro Fertilization and Embryo Transfer* (28), and the *International Journal of Fertility* (21). This is also the order of the impact factors of these journals. The general medical journals (*Lancet, JAMA, New England Journal of Medicine, British Medical Journal*) have the highest impact factors, but publish only a few randomized controlled trials on the treatment of infertility. Of the specialist journals, those publishing the most randomized controlled trials have the highest associated impact factors.

Figure 3. Country of Origin of Randomized Controlled Trials



Analysis of the topics investigated shows that variations of assisted-conception techniques (e.g., IVF and gamete intrafallopian transfer [GIFT]) have been the most frequent subject of unbiased assessment, followed by the treatment of endometriosis, anovulation, polycystic ovarian disease, oligoasthenozoospermia of unknown cause, unexplained infertility, and tubal damage (Figure 4). Structured reviews of randomized controlled trials concerning unexplained infertility, endometriosis, and selected assisted-conception techniques have been carried out by the McMaster group, whereas the Leeds group has compiled detailed overviews and meta-analyses within the area of male subfertility (see also "Treatment of Male Infertility: Is it Effective? A Review and Meta-Analyses of Published Randomized Controlled Trials," in this volume).

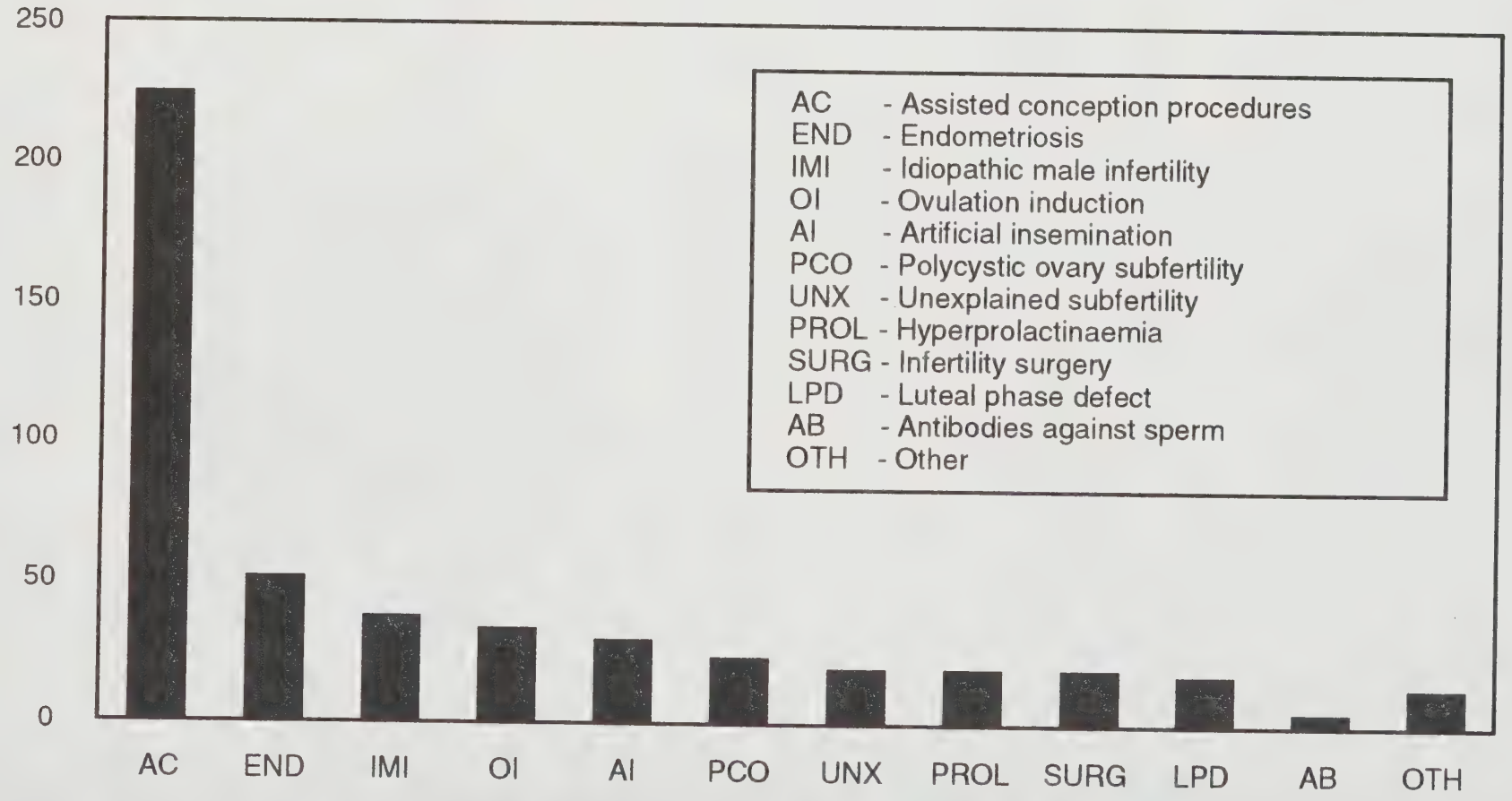
The method of randomization was described in only 288 (57%) of the 501 studies. In 59 of these, the described method could have led to prior knowledge of group allocation by the investigator (e.g., date of birth, case record number, date of presentation, alternate assignment), which, in turn, could have affected the decision regarding entry of patients into the trial. This "pseudo-" or "quasi-randomization" can be an important source of selection bias (Olive 1986).

In nine publications, randomized methodology in the design and execution of the trial was used, but instead of comparing outcome results between the two arms of the trial, pre- and post-treatment results within the same arms were analyzed and discussed (De Almeida et al. 1985; Bhathena and Patel 1986; Bhathena et al. 1987; Gadir et al. 1990a) or analysis was based on other groups rather than the randomized ones (Hinton et al. 1979; Huang et al. 1984; Pampiglione et al. 1988; Buvat et al. 1989; McFaul et al. 1989a).

The control group received no treatment in 73 (15%) of the studies, placebo treatment in 92 (18%) studies, some alternative form of treatment in 262 (52%) studies, or a combination of the above when multiple comparison groups existed in 74 (15%) studies. Crossover design was used in 103 (21%) of the trials. Double-blind design was used in 118 (24%) trials — not surprisingly, these were mainly drug trials. Single-blind design was used in four trials; in three of these trials the treatment was blind to the patient (Roumen et al. 1984; Giovenco et al. 1987; Harrison 1988) and in one trial the treatment was blinded for the physician (Mitchell et al. 1989). Factorial design was used in five trials (Jansen 1985; Salat-Baroux et al. 1988c; Gindoff et al. 1990; Homburg et al. 1990c; Mansour et al. 1990). There were two additional trials (Parinaud et al. 1987a; Shaw et al. 1987) in which randomization was used for the primary but not for the secondary allocation.

The issue of the power of the study was raised by 16 authors, but only 11 (Rock et al. 1984a; MacLennan et al. 1985; Belaisch-Allart et al. 1987; Thomas and Cooke 1987a, 1987b; Barratt et al. 1989; Brinsmead et al. 1989; Daures et al. 1990; Federman et al. 1990; Johnson and Pearce 1990;

Figure 4. Randomized Controlled Trials by Subject



Kubik et al. 1990) gave details of a full power calculation based on a prior specification of delta (the magnitude of the treatment effect sought) and the risk of accepting the null hypothesis in error (beta error). Six of these trials did not reach the required calculated number of patients.

Sequential analysis design, which would identify an unexpectedly effective treatment with a smaller number of subjects, was seldom used. Seven trials appeared to be open in that the author stated that the trial was stopped or modified when the results reached a certain level of significance, but only three of these trials (Johnson et al. 1966; Rock et al. 1984a; Johnson and Pearce 1990) used standard sequential design, including a clearly defined stopping rule. Pregnancy diagnosed during the first trimester was the outcome in all of these "open" trials.

Twenty-nine (5.8%) of the studies were multicentre collaborative trials, eight of these involving international collaboration (Rock et al. 1984b; Comhaire et al. 1986; Henzl et al. 1988; Gianaroli et al. 1989; INTERCEED [TC7] 1989; Menezo et al. 1989; World Health Organization [WHO] Task Force 1989; Rolland and Van der Heijden 1990). The average number of participating patients in these multicentre trials was considerably higher than in the single-centre trials: 175 (ranging from 24 to 716) versus 64. The number of participating centres ranged from 2 to 13, with an average of 6.

Sometimes individual participating centres publish their results separately from the main report (e.g., Claesson and Bergquist (1989) and Bergquist (1990) reporting on 24 patients in Sweden, Valimaki et al. (1989) and Ylikorkala et al. (1990) on 18 patients in Finland, Kennedy et al. (1990) on 35 patients in Oxford, and Shaw (1990) on 82 patients in London, all participating in the multicentre trial of 194 patients comparing nafarelin and danazol for endometriosis, published by Rolland and Van der Heijden (1990)), and care must be taken to ensure that these patients are not included twice when meta-analysis is performed.

Only 27% of the 287 trials in which pregnancy was an outcome reported a statistically significant difference between study and control couples at the 5% level. This may be a result, in part, of the insufficient sample sizes of most trials, so that smaller, but nevertheless worthwhile, improvements were not detected.

"Successful" treatment (in the form of pregnancy) was not defined in 200 (70%) of the pregnancy trials. Diagnosis of pregnancy was through biochemical means in 21 (7%) of the trials, ultrasound scanning (gestational sac, fetal heart, or not specified) in 51 (18%) of the trials, and determination of a "clinical" or "viable" pregnancy in 15 (5%) of the trials.

Cumulative conception curves to display the pregnancy results were used in 38 trials, and 23 of these used life-table analysis.

The source of funding was stated in 185 (37%) of the trials. Of these, 48% were funded by a drug company, 36% by a national research body, 7% by an international research body (e.g., WHO), 7% by university grants, and 2% by hospital funds.

Discussion

Searching for Infertility Trials

A MEDLINE search under the keyword "random allocation" revealed a total of 28 677 randomized trials up to the end of 1990. The Oxford Database of Perinatal Trials contained more than 5 000 references to reports on controlled trials, and MEDLINE underestimated the total number of randomized studies in perinatology by about 50% (Chalmers et al. 1989). In the present assessment, the MEDLINE search underestimated the number of randomized infertility trials by a factor of six (80 of the 501 randomized trials [16%] were identified via MEDLINE). When the characteristics of the trials identified through MEDLINE were compared with those of trials identified through other sources, no difference was found in the methodological quality criteria, sample size, or frequency of "positive" results. Some retrieval bias may occur insofar as MEDLINE identifies multicentre trials and trials originating from larger countries more readily.

No doubt studies have been missed in the present investigation; therefore, experts are invited to bring to the authors' attention those trials that have been omitted, along with any unpublished trials or trials in progress, so that they can be appended to the data base that is being assembled.

Randomized Trials in Infertility Treatment

- Judging the effectiveness of infertility treatment by comparing outcomes for similar patients reported in the literature and by trying to provide control through statistical adjustment for differences in prognostic variables is inadequate because it is only possible to adjust for known sources of selection bias. The wide variation in reported results for similar infertility treatments among apparently similar patients underscores the need for randomized methodology. Fertility rates after danazol treatment of endometriosis, for example, range from 23 to 50%, even among patients who seem to have similar prognostic features (Schmidt 1985).

Practical problems relating to sample size are less severe in the case of infertility treatment than in the investigation of many other topics. Some important questions in obstetrics require studies involving 100 000 subjects or more (Lilford 1987). In the case of infertility research, much smaller sample sizes would be adequate, even when pregnancy is used as an outcome, because a much larger absolute improvement in outcome can realistically be expected following treatment for infertility compared, for example, with perinatal medicine. Thus, to detect a change in pregnancy rate from 10 to 15%, with a power of 80% and a "p" value of less than 0.05, 700 patients would be required in each arm of a randomized trial (Table 1). If alpha and beta are both set at 10% (Lilford and Johnson 1990), then 750 patients would be needed in each group. In many cases, two or more treatments are compared when neither has been proven effective — it is preferable to have a placebo arm in such cases. Although pregnancy is the

primary outcome of infertility treatment, other outcomes are not without interest — multiple pregnancy, psychological strain, and financial costs are all important end points.

Table 1. Sample Sizes Suggested for Infertility Trials

		Incremental success rate — delta (%)				
		+2	+5	+10	+15	+20
Control	50	9 870	1 572	390	168	95
success	30	8 450	1 383	360	161	90
rate	20	6 550	1 100	300	140	80
(%)	10	3 870	690	200	97	60

Based on alpha of 5% and beta of 20%.
An equal alpha and beta give slightly larger numbers (Lilford and Johnson 1990).
The results are expressed as the number of subjects required per group, using a two-tailed test.

Bias in Reported Trials

Even in randomized trials, bias (systematic error) can occur. Therefore, schemes have been developed to assess the methodology and quality of randomized trials (reviewed by Chalmers [1989]). Bias can be introduced at treatment assignment, during the course of treatment, or when the outcomes are assessed.

The use of a suitable method of randomization should ensure unbiased treatment allocation. In nearly half of the infertility trials studied the method of randomization was not specified, and more than a fifth of the remainder were based on pseudo-randomization as described earlier. Third-party randomization to reduce cheating was rarely used. Psychological effects among patients or co-intervention by physicians could theoretically influence the outcome of treatment, but many infertility treatments involve physical interventions that cannot be easily masked to eliminate bias during trials. For example, a randomized trial investigating the effect of general anaesthesia (GA) on the success of embryo transfer (Van der Ven et al. 1988) showed an improved pregnancy rate in the GA group, but continuous observation after the trial (when GA was administered for every embryo transfer) demonstrated pregnancy rates similar to those in the non-GA group during the trial. This may have been the result of random error or the inclusion of worse-risk patients after the study, but it might also have been, at least in part, an effect of

co-intervention during the trial. Similarly, blind assessment of the outcome is often impractical and arguably not important when assessing the relatively hard outcome of pregnancy.

The birth of a healthy child is the best end point because this is the parents' objective and because infertility treatment may be associated with increased fetal or neonatal morbidity. For example, Van de-Helder et al. (1990) found that diagnosis of pregnancy by ultrasonographic detection of a fetal heart early in the first trimester exaggerated the benefits of "downregulation" of the pituitary prior to ovulation induction.

The sample size of randomized trials can be reduced by using a crossover design, but this method overestimates the beneficial effects of interventions, such as infertility treatment, when patients fail to enter the second part of the trial specifically because of the selective success of one of the treatments during the first phase of the trial (Hills and Armitage 1979). However, factorial design seems appropriate for randomized infertility trials, especially in the field of assisted conception.

Sequential analysis was seldom used, but there is cause for concern over the use of this statistical technique to study infertility for two reasons. First, there is no completely satisfactory stopping rule when frequency statistics are used. Secondly, sequential trials are practical only when the interval between the intervention and outcome is short. A consequence of this drawback, in the context of infertility research, is that the diagnosis of pregnancy in these trials is made during the first trimester rather than after delivery of a healthy child (Rock et al. 1984a).

Another factor that may be overlooked by clinicians carrying out infertility trials is the importance of keeping patients in their originally assigned groups. This is a problem when randomization is carried out much earlier than the intervention and when there is an appreciable drop-out rate in the intervening phase. This was seen, for example, when luteal support was given on the basis of randomization at the beginning of assisted-conception cycles — some authors reported on the original groups (thereby risking imprecision), whereas others analyzed only those who came to embryo transfer (thereby risking bias). Randomization at the time of embryo transfer would be more appropriate for such patients.

When pregnancy rates are reported on a "per patient" basis, duration and completeness of follow-up should be stated. Under these circumstances, pregnancy rates are best displayed as cumulative conception curves using life-table analysis techniques. An outcome for patients is not only "if" pregnancy occurs but also "when" it occurs.

A subtle form of bias has crept into the prevailing non-randomized literature in which the success rates of artificial reproductive techniques among couples from the same original cohort are compared on the basis of cycles during which they have received or have not received the intervention. Clinicians are likely (consciously or subconsciously) to select couples with the best prognosis for repeat treatments. As a result, the comparison between those receiving and not receiving treatment becomes progressively biased. This is referred to as attenuation bias, which is a risk

whenever there is an appreciable drop-out rate between successive cycles of treatment. Similarly, when results are given on a "per cycle" basis in randomized trials, it is preferable to re-randomize couples who go on to second or subsequent treatment cycles for each cycle, as is done, for example, in the trial of Dodson et al. (1987), which compares two regimens of ovulation induction in polycystic ovarian disease. Again, this is done because patients receiving follow-up treatment may become progressively different from those in the original cohort, and it is possible that this factor would operate unequally between groups. This issue was covered explicitly in the study of Imoedemhe et al. (1987), in which bias was possible because only "good" responders (to a certain ovarian stimulation protocol for IVF) were allowed to continue in the trial, but without further randomization.[1] If patients are not re-randomized in subsequent cycles, but continue to receive the same treatment to which they were originally assigned, the results should be analyzed on a per patient, not a per cycle, basis.

Structured Overviews and Meta-Analysis

Unfortunately, the majority of individual trials are much too small to exclude possible worthwhile treatment effects; however, meta-analysis may be possible in some cases. Previously unproven but widely used treatments, such as clomiphene treatment of the female partner in unexplained infertility, have recently been studied scientifically (Harrison and O'Moore 1983; Fisch et al. 1989a; Deaton et al. 1990; Glazener et al. 1990). The four individual trials were all "negative," but, when combined in meta-analysis, they showed a statistically significant doubling of the pregnancy rate.

In collaboration with our colleagues at McMaster University, structured overviews and quantitative meta-analyses on selected topics, such as male infertility and regimens for ovulation induction, are being compiled. However, many more trials are needed to provide clear information about the effectiveness of most treatments. For example, only one trial examined the effect of varicocele ligation for oligozoospermia (Nilsson et al. 1979), with a negative result at the 5% level. The use of corticosteroids for infertility associated with antisperm antibodies has been investigated by four authors in trials in which pregnancy was an outcome (Katz and Newill 1980; Luisi et al. 1982; Haas and Manganiello 1987; Hendry et al. 1990). The trial by Hendry et al. (1990) was a crossover design, and the data in the trial by Luisi et al. (1982) were insufficient to calculate an odds ratio. Here and elsewhere is a need for better-quality studies.

Where meta-analysis is possible because the same theme has been investigated a number of times, the conclusions that can be drawn are less

[1] Purists might prefer that "per cycle" pregnancy rates be based on the first cycle of treatment only. Again, this is based on the changing chances of success in subsequent cycles and the further possibility that some treatments might be particularly successful in good- or poor-risk subjects. This argument seems excessively theoretical and not important in a practical sense because assisted-conception programs in "real life" include patients who have experienced varying numbers of previous attempts.

secure than one might have hoped because of the poor quality of many studies. The use of anti-estrogens for the treatment of idiopathic oligoasthenozoospermia is an example. The meta-analysis of all trials (M3, Figure 5) suggests a strong treatment effect. Closer examination of the data, however, shows that the results seem to be unduly influenced by the studies of Micic and Dotlic (1985) and Check et al. (1989a). The method of randomization was not stated in the Micic and Dotlic (1985) trial and the trial of Check et al. (1989a) was not truly randomized. Furthermore, the study by Check et al. (1989a) is an "outlier," which destroys the homogeneity of the meta-analysis (Breslow-Day test = 16.4, p = 0.02). Meta-analysis, excluding these studies and the crossover studies of Wang et al. (1983) and Ainmelk et al. (1987) (M1, Figure 5), does not show a statistically significant effect, with an odds ratio of 1.27 and 95% confidence interval of 0.67-2.40 and a Breslow-Day test showing homogeneity (p = 0.16).

Publication Bias

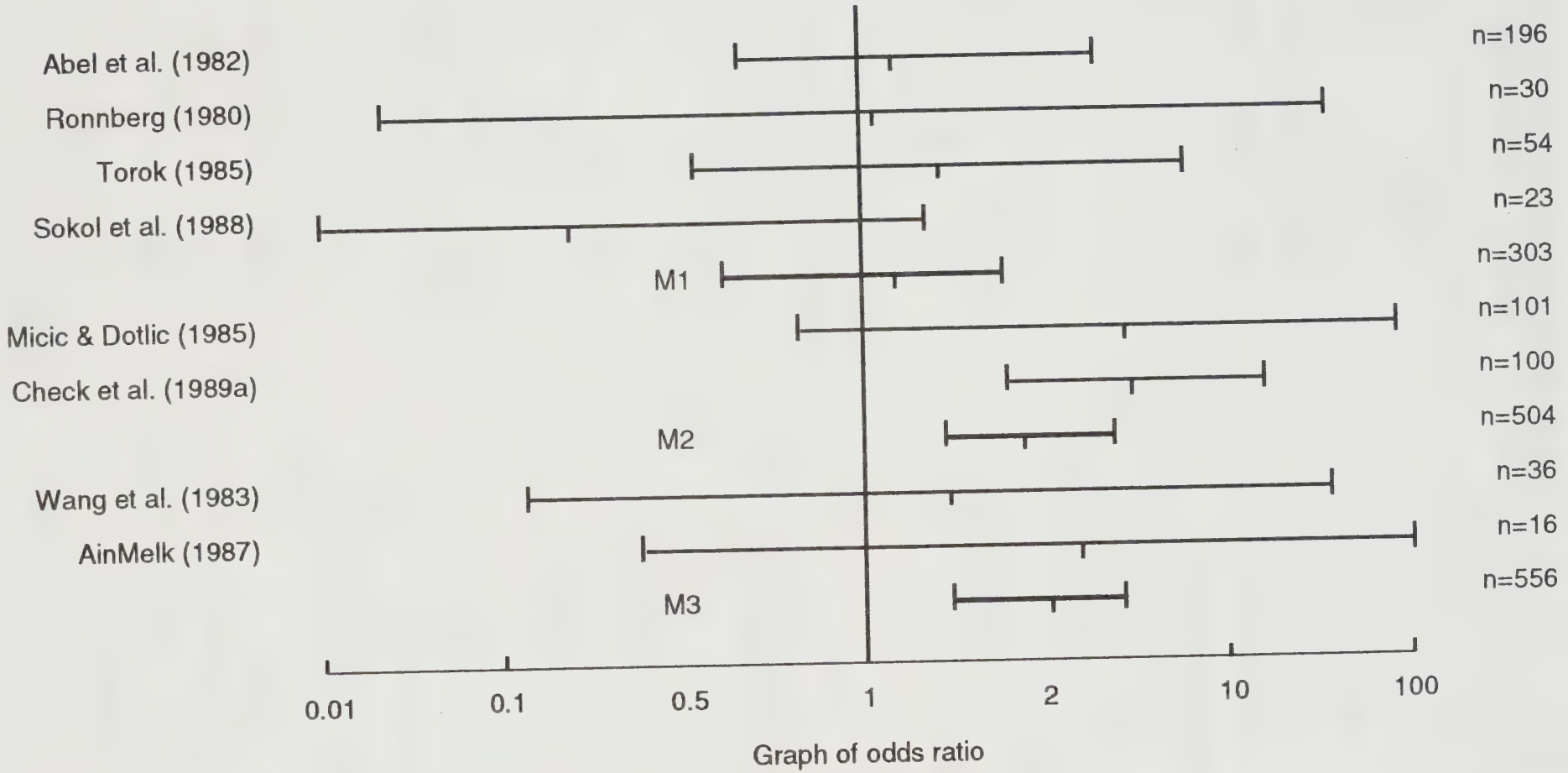
There is growing evidence of publication bias in clinical research, whereby "positive" trials are more likely to be accepted for publication than trials showing no differences among the treatments tested (Easterbrook 1991). However, less than 30% of infertility trials showed a statistically significant improvement in pregnancy rates, leaving little room for publication bias to come into play. It is, however, interesting to note that 6 of the 76 studies with positive results were reported from the same institution (Nowroozi et al. 1987; Check et al. 1988 [double trial], et al. 1989a [double trial], 1989b).

Conclusions

The ideal infertility study includes a clearly defined cohort of patients, is powerful (usually multicentre), is single phase, uses true randomization (by a third party or computer), and has a high degree of follow-up over a sufficient time period during which unambiguous confirmation of pregnancy (or, even better, the birth of a live child) is an end point. A study that comes close to meeting these rigorous criteria in the field of infertility is the second trial of Hargreave et al. (1984), which compared mesterolone versus vitamin C for male infertility.

Only 29 of the studies reviewed in the present investigation were multicentre studies. However, there are numerous national organizations, and one international organization, concerned with the study of infertility. Even though an attempt by an individual department to become the coordinating centre for randomized trials might fail due to natural rivalries, the present authors suggest that multicentre trials should be coordinated along national or international lines through such organizations.

Figure 5. Meta-Analysis of Randomized Trials of Anti-Estrogens vs. Placebo/Vitamin C for Oligospermia



Note: M_1 refers to truly randomized, one-phase trials only (in crossover trials, only data from the first phase are used). M_2 includes quasi-randomized trials and trials for which the method of randomization was not specified. M_3 includes all of the above trials and crossover studies (where no separate data from the first phase are available).

Appendix 1. Journals Searched Manually (1966-1990), with the Impact Factor (for 1988, 1990) and Number of Randomized Trials Identified per Journal

	Impact factor		Number of randomized trials	
Journal	**1990**	**1988**	**Female**	**Male**
Acta Endocrinologica	1.43	1.33	7	1
Acta Europaea Fertilitatis	*	*	1	5
Acta Obstetricia et Gynecologica Scandinavica	0.37	0.43	6	1
American Journal of Obstetrics and Gynecology	2.09	1.92	15	1
American Journal of Reproductive Immunology	2.17	1.25	-	-
Andrologia	0.43	0.46	-	20
Archives of Andrology	0.36	0.48	-	16
Australian and New Zealand Journal of Obstetrics and Gynaecology	0.18	0.29	2	-
Biology of Reproduction	2.68	2.52	-	3
British Journal of Obstetrics and Gynaecology	1.65	1.63	7	1
British Journal of Urology	0.79	0.74	-	4
British Medical Journal	3.76	3.14	5	-
Clinical Endocrinology	2.11	2.23	10	4
Clinical Reproduction and Fertility	*	*	6	2
European Journal of Obstetrics & Gynecology and Reproductive Biology	0.51	0.37	10	1
Fertility and Sterility	2.49	2.11	109	36
Gynecological Endocrinology	0.43	*	12	-
Gynecologic and Obstetric Investigation	0.49	0.58	1	2
Hormone Research	0.67	1.04	3	1
Human Reproduction	1.46	0.77	40	18

Appendix 1. (*cont'd*)

Journal	Impact factor		Number of randomized trials	
	1990	1988	Female	Male
International Journal of Andrology	1.25	1.17	-	13
International Journal of Fertility	0.47	0.34	11	10
International Journal of Gynaecology and Obstetrics	0.16	0.31	1	-
JAMA	5.46	5.28	-	1
Journal of Andrology	1.58	2.07	-	5
Journal of Clinical Endocrinology and Metabolism	3.93	4.09	16	-
Journal of Endocrinology	2.81	2.39	-	-
Journal of Gynaecologic Endocrinology	*	*	12	-
Journal de Gynécologie obstétrique et Biologie de la Reproduction	*	*	5	2
Journal of Gynaecologic Surgery	0.27	*	-	-
Journal of In Vitro Fertilization and Embryo Transfer	0.74	1.67	27	1
Journal of Obstetrics and Gynaecology		0.10	-	-
Journal of Reproduction and Fertility	2.16	2.33	4	10
Journal of Reproductive Immunology	2.13	1.67	-	-
Journal of Reproductive Medicine	0.47	0.62	3	-
Journal of Urology	1.76	1.87	-	3
Lancet	15.3	14.5	6	7
New England Journal of Medicine	22.68	21.2	1	-
Obstetrics and Gynecology	1.91	1.90	10	1
Surgery, Gynecology and Obstetrics	1.13	1.07	-	1
Urology	0.57	0.64	-	1

* Not covered in the *Journal Citation Reports*, Institute for Scientific Information, Philadelphia, Pennsylvania, USA.

Appendix 2A. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome on a Per Patient Basis

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Pryor et al.	London UK 1978	Arginine vs. placebo for oligospermia	64	0.81 (0.07-8.80)+	TR	2	33	2	27	NS	3
Hovatta et al.	Helsinki Finland 1979	Bromocriptine vs. placebo for oligospermia	40	0.47 (0.01-7.66)	TR	1	19	2	18	NS	3
Nilsson et al.	Goteborg Sweden 1979	Ligation of varicocele or not for oligospermia associated with varicocele	96	0.39 (0.09-1.60)	NS	4	47	8	37	NS	36-74
Paulson	Durham USA 1979	Cortisone acetate vs. clomiphene for oligospermia	40	0.20 (0.02-1.38)	PR	2	18	7	13	NS	9
Schill	Munich Germany 1979	Kallikrein vs. placebo for oligospermia	135	3.05 (0.89-10.95)	TR	14	34	5	37	NS	12

Katz and Newill	London UK 1980	Comparison of two steroid regimes for male immunological infertility		3641)#							
Ronnberg	Oulu Finland 1980	Clomiphene vs. placebo for normo- and oligospermia	30	1.07 (0.03-44.94)+	TR	1	13	1	14	NS	3
Bedford and Elstein	Manchester UK 1981	Kallikrein vs. placebo for oligospermia	29	0.75 (0.17-32.55)+	TR	1	12	1	9	NS	3
Sharlip	San Francisco USA 1981	Comparison of two surgical techniques of vasovasostomy	19	0.66 (0.04-8.34)	PR	6	3	6	2	NS	13
Abel et al.	Multicentre Scotland 1982	Clomiphene vs. vitamin C for male infertility	196	1.46 (0.57-3.76)	TR	15	78	10	76	NS	9
AinMelk et al.	Sherbrooke Canada 1982	Bromocriptine vs. placebo for oligospermia	16	1.00 (0.02-47.27)+	TR	0	6	0	6	NS	4
Aafjes et al.	Rotterdam Netherlands 1983	Mesterolone vs. placebo for oligospermia	59	0.94 (0.18-4.73)+	TR	4	23	5	27	NS	6
Lunglmayr et al.	Vienna Austria 1983	Bromocriptine vs. placebo for oligospermia	50	1.00 (0.09-11.15)TR	TR	2	23	2	23	NS	3

Appendix 2A. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Baker et al.	Melbourne Australia 1984	Erythromycin vs. placebo for asthenospermia	90	3.18 (0.50-23.96)+	TR	6	34	2	35	NS	2
Hargreave et al.	Multicentre Scotland 1984	Mesterolone vs. vitamin C for male infertility	368	1.06 (0.58-1.91)	TR	34	142	28	124	NS	12
Izzo et al.	Pisa Italy 1984	Kallikrein vs. placebo for oligospermia	29	3.46 (0.25-98.30)#	TR	2	13	0	14	NS	3
Iddenden et al.	London UK 1985	Fresh vs. cryopreserved semen for AID	60	0.73 (0.21-2.47)*	NS	10	10	23	17	NS	12
Micic and Dotlic	Belgrade Yugoslavia 1985	Clomiphene vs. no treatment for oligospermia	101	7.36 (0.87-162.9)#	NS	7	49	0	45	NS	9
Micic et al.	Belgrade Yugoslavia 1985	Kallikrein vs. no treatment for oligospermia	75	8.37 (0.99-184.6)#	NS	9	36	0	30	NS	6

Semczuk et al.	Lublin Poland 1985	Comparison of two doses of clomiphene (50 mg vs. 100 mg) for oligospermia	22	4.16 (0.33-110.9)#	NS						
Torok	Kecskemét Hungary 1985	Tamoxifen vs. placebo for oligospermia	54	2.20 (0.53-9.34)	TR	9	18	5	22	NS	12
Comhaire et al.	Multicentre International 1986	Doxycycline vs. placebo for oligospermia with genital tract infection	33	1.33 (0.07-42.00)	TR	2	18	1	12	NS	5
Haas and Manganiello	Oklahoma City USA 1987	Methylprednisolone vs. placebo for male immunological infertility	43	2.47 (0.19-69.26)	TR	3	17	1	14	NS	3
Melis et al.	Pisa Italy 1987	AIH + clomiphene vs. AIH only for oligospermia	90	0.86 (0.19-3.78)+	NS	5	43	5	37	NS	6
Hogerzeil et al.	Amsterdam Netherlands 1988	Home vs. clinic inseminations for AID	53	0.96 (0.28-3.27)+	NS	13	16	11	13	NS	6
Micic	Belgrade Yugoslavia 1988	Kallikrein and antibiotics vs. antibiotics only for oligospermia with genital tract infection	120	2.24 (0.88-5.81)	NS	21	43	10	46	NS	3

Appendix 2A. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Sokol et al.	Los Angeles USA 1988	Clomiphene vs. placebo for oligospermia	23	0.12 (0.01-1.87)	TR	1	10	4	5	NS	12
Barratt et al.	Sheffield UK 1989	Urinary LH vs. BBT for timing of insemination in AID	53	1.47 (0.34-6.53)	NS	7	20	5	21	NS	6
Check et al.	Philadelphia USA 1989b	Clomiphene vs. vitamin C for the male partner in unexplained infertility	100	7.25 (2.59-20.90)	PR	29	21	8	42	NS	8
Painvain et al.	Rome Italy 1989	Comparison of two different volumes of frozen sperm for AID	210	2.91 (1.52-5.58)	NS	55	55	23	67	BIOCH	8
Pusch	Graz Austria 1989	Oral testosterone-undecanoate vs. placebo for oligospermia	60	1.62 (0.34-7.98)	TR	6	24	4	26	NS	3

World Health Organization Task Force	Multicentric International 1989	placebo for oligospermia		5.45)*							
Hovatta et al.	Helsinki Finland 1990	DIPI vs. IUI combined with ovarian stimulation for male unexplained and endometriosis-associated infertility	124	0.69 (0.29-1.64)	NS	15	48	19	42	NS	4
Micic et al.	Belgrade Yugoslavia 1990	Kallikrein vs. no treatment for oligospermia associated with varicocele	65	2.82 (0.46-21.73)	NS	7	31	2	25	NS	3

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: AID, artificial insemination with donor sperm; AIH, artificial insemination with husband's sperm; BBT, basal body temperature, LH, luteinizing hormone; DIPI, direct intraperitoneal administration; IUI, intrauterine insemination.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes, one was added to all the groups);
*, more treatment groups were assigned in the trial, but they are combined here to make a 2×2 table.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; BIOCH, biochemical.

Appendix 2B. Randomized Trials for Female Infertility Treatment: Pregnancy Outcome on a Per Patient Basis

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Cudmore and Tupper	Halifax Canada 1966	Clomiphene vs. placebo for anovulation	29	1.53 (0.08-50.15)+#	TR	1	12	0	9	NS	3
Johnson et al.	Cincinnati USA 1966	Clomiphene vs. placebo for anovulation	65	6.82 (0.73-159.6)+#	TR	5	28	0	32	NS	1
Swolin	Goteborg Sweden 1967	Intraperitoneal instillation of hydrocortisone or not after tubal surgery	108	1.87 (0.57-6.21)	PR	11	22	8	30	NS	?
Denber and Roland	New York USA 1969	Tybamate vs. placebo for psychosomatic symptoms in infertility patients	35	0.43 (0.01-7.32)	TR	1	16	2	14	NS	2
Echt et al.	Indianapolis USA 1969	Clomiphene vs. placebo for luteal-phase	19	2.00 (0.10-66.69)#	TR	1	9	0	9	NS	2

	USA 1973	hCG with or without estradiol vs. clomiphene only for anovulation		2.76)*							
Harrison et al.	London UK 1975	Doxycycline vs. placebo or no treatment for unexplained infertility	88	1.08 (0.28-4.09)*	TR	5	25	9	49	NS	7
Comninos	Athens Greece 1977	Comparison of two methods of salpingostomy for bilateral tubal occlusion	30	0.50 (0.07-3.37)	NS	3	12	5	10	NS	24
Harrison et al.	Dublin Ireland 1979	Bromocriptine vs. placebo for unexplained infertility	30	0.83 (0.12-5.52)	TR	4	12	4	10	NS	6
van Dijk et al.	Leiden Netherlands 1979a	Danazol® vs. placebo for unexplained infertility	40	6.70 (0.66-163.5)#	NS	5	16	0	18	NS	6
Wright et al.	London UK 1979	Bromocriptine vs. placebo for unexplained infertility	49	1.48 (0.32-6.80)	TR	7	17	5	18	NS	6
Noble and Letchworth	Winchester UK 1980	Danazol® vs. enavid for endometriosis	50	2.25 (0.36-14.83)	PR	9	7	4	7	NS	?

Appendix 2B. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Biberoglu and Behrman	Royal Oak USA 1981	Low- vs. high-dose Danazol® for endometriosis	32	0.61 (0.05-5.84)*	TR	2	13	3	12	NS	19 (mean)
DeCherney and Kase	New Haven USA 1981	Microsurgery vs. Rock-Mulligan prosthesis for bilateral tubal occlusion	18	2.80 (0.25-36.20)	PR	4	5	2	7	NS	24
Moore et al.	Multicentre USA 1981	Low- vs. high-dose Danazol® for endometriosis	38	3.67 (0.46-35.00)*	NS	6	9	2	11	NS	6-24
Balasch et al.	Barcelona Spain 1982	Dehydrogesterone vs. no treatment for luteal-phase defect	32	2.27 (0.28-22.04)	NS	5	11	2	10	NS	3
		Progesterone vs. no treatment for luteal-phase	32	2.27 (0.28-22.04)	NS	5	11	2	10	NS	3

et al.	USA 1982	dose Danazol® for endometriosis		14.64)*							
Seibel et al.	Boston USA 1982	Danazol® vs. observation for endometriosis	65	0.25 (0.05-1.09)	TR	4	16	14	14	NS	6
Harrison and O'Moore	Dublin Ireland 1983	Clomiphene plus hCG vs. placebo plus hCG for unexplained infertility	30	4.92 (0.41-131.3)+#	NS	3	12	0	15	BIOCH	6
Schwabe et al.	Madison USA 1983	Oil vs. aqueous contrast medium for hysterosalpingo-graphy	198	2.02 (0.65-6.36)	PR	11	45	7	58	NS	4
Rock et al.	Baltimore USA 1984a	Microsurgery vs. loupe for tubal reanastomosis	72	0.74 (0.22-2.45)	TR	26	10	28	8	NS	24
Rock et al.	Multicentre International 1984b	Post-operative hydrotubation or not after tubal surgery	206	1.12 (0.53-2.35)*	TR	26	94	17	69	NS	24-48
Garcia et al.	Philadelphia USA 1985	Clomiphene vs. placebo for anovulation	49	5.00 (0.79-39.96)+	TR	8	16	2	20	NS	5

Appendix 2B. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Jansen	Sidney Australia 1985	Intraperitoneal dextran vs. placebo following tubal surgery	164	0.85 (0.43-1.69)	TR	27	51	33	53	NS	1-18
		Steroids or not following tubal surgery	164	1.02 (0.51-2.02)	TR	32	55	28	49		
Tulandi and Vilos	London Canada 1985	CO_2 laser vs. microdiathermy for bilateral tubal occlusion	67	1.39 (0.40-4.82)	NS	11	26	7	23	NS	24
Alper et al.	Ottawa Canada 1986	Oil- vs. water-soluble contrast media for hysterosalpingography	131	1.31 (0.51-3.37)	TR	14	32	15	45	USS-NS	6

	USA 1986	vs. clomiphene for luteal-phase defect		6.85)+							
Seiler et al.	Cleveland USA 1986	Laparoscopic cauterization vs. Danazol® for endometriosis	90	1.45 (0.57-3.70)	PR	20	25	16	29	NS	7
Tulandi	Montreal Canada 1986	CO_2 laser vs. microdiathermy in salpingo-ovariolysis for periadnexal adhesions	63	1.07 (0.35-3.26)	NS	16	14	17	16	NS	24
Melis et al.	Pisa Italy 1987	AIH plus clomiphene vs. AIH only for unexplained infertility	27	0.80 (0.02-14.0)+#	NS	0	9	1	15	NS	6
Melis et al.	Pisa Italy 1987	AIH plus clomiphene vs. AIH only for cervical infertility	5	0.75 (0.01-45.92)+#	NS	0	3	0	2	NS	6
Miyake et al.	Tokushima Japan 1987	Luteal-phase clomiphene vs. no treatment for luteal-phase defect (in patients on follicular-phase clomiphene for anovulation)	75	3.11 (0.75-13.68)	NS	9	26	4	36	NS	3

Appendix 2B. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of random-ization	Treatment group		Control group		Diag-nosis of preg-nancy	Duration of follow-up (months)
						No. preg-nant	No. not preg-nant	No. preg-nant	No. not preg-nant		
Nowroozi et al.	Philadelphia USA 1987	Laparoscopic coagulation vs. observation for endometriosis	123	6.84 (2.75-17.39)	PR	42	27	10	44	NS	8
Rossmanith et al.	Ulm Germany 1987	Pulsatile subcutaneous vs. intramuscular hMG for clomiphene-resistant polycystic ovary syndrome	10	1.00 (0.02-57.70)	NS	1	4	1	4	NS	2
Telimaa et al.	Oulu Finland 1987	Danazol® vs. medroxypro-gesterone acetate for endometriosis (after conservative surgery)	16	0.56 (0.39-7.23)	TR	2	6	3	5	NS	6
Thomas and Cooke	Sheffield UK	Gestrinone vs. placebo for	40	1.08 (0.19-6.26)	TR	5	15	4	13	NS	12

Bayer et al.	Boston USA 1988	Danazol® vs. no treatment for endometriosis		1.71)							
Check et al.	Philadelphia USA 1988	Progesterone vs. clomiphene/ hMG for luteal-phase defect with immature follicles	22	0.14 (0.01-1.27)	PR	3	9	7	3	NS	6
Check et al.	Philadelphia USA 1988	Progesterone vs. clomiphene/ hMG for luteal-phase defect with mature follicles	58	27.4 (5.41-162.2)	PR	24	7	3	24	NS	6
de Boer et al.	Nijmegen Netherlands 1988	Oil vs. aqueous contrast medium for hystero-salpingography	175	1.48 (0.73-2.99)	NS	30	57	23	65	NS	6
Dlugi et al.	Boston USA 1988	Buserelin vs. Danazol® for endometriosis	26	2.46 (0.18-69.16)#	TR	3	12	0	7	NS	2
Henzl et al.	Multicentre International 1988	Nafarelin® (two dosages) vs. Danazol® for endometriosis	236	1.22 (0.56-2.70)*	TR	42	62	16	29	NS	12
Telimaa	Oulu Finland 1988	Medroxyprogest erone acetate vs. placebo for endometriosis	31	0.93 (0.17-4.95)	NS	7	10	6	8	NS	30

Appendix 2B. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Burry et al.	Portland USA 1989	Nafarelin® (two dosages) vs. Danazol® (two dosages) for endometriosis	53	6.00 (0.98-46.86)*	TR	15	15	2	12	NS	24
Check et al.	Philadelphia USA 1989a	Bromocriptine vs. progesterone for "pure" luteal-phase defect (in hyperprolactinemic patients)	60	0.06 (0.01-0.25)+	PR	5	25	23	7	NS	8
Check et al.	Philadelphia USA 1989a	Bromocriptine vs. progesterone for luteal-phase defect with immature follicles (in hyperprolactinemic patients)	40	13.2 (2.3-88.37)+	PR	14	6	3	17	NS	8

Dmowski	Chicago USA 1989	Buserelin vs. Danazol® for endometriosis	36	3.47)							
Fedele et al.	Milan Italy 1989a	Gestrinone vs. Danazol® for endometriosis	39	0.79 (0.17-3.70)	NS	6	13	7	12	NS	18
Fedele et al.	Milan Italy 1989b	Buserelin vs. Danazol® for endometriosis	62	1.27 (0.40-3.99)	NS	13	17	12	20	NS	18
Fisch et al.	Toronto Canada 1989a	Clomiphene with or without hCG vs. placebo with or without hCG for unexplained infertility	177	2.58 (0.69-10.33)*	TR	10	66	4	68	USS-FH	4
Iffland et al.	London UK 1989	Danazol® vs. placebo for unexplained infertility	31	0.66 (0.02-11.39)#	TR	0	11	1	16	NS	12
Querleu et al.	Multicentre France 1989	Corticosteroids and/or noxytioline in the prevention of adhesion formation following tubal surgery	126	1.58 (0.56-4.56)*	NS	30	65	7	24	NS	36
Tulandi et al.	Montreal Canada 1989	Second-look laparoscopy or not after tubal surgery	74	1.22 (0.43-3.43)	NS	16	20	15	23	NS	36

Appendix 2B. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Tummon et al.	Chicago USA 1989	Leuprolide vs. Danazol® for endometriosis	15	3.50 (0.24-63.6)	NS	7	3	2	3	NS	12
Cabau et al.	Multicentre France 1990	Cyclofenil vs. placebo for ovulatory, cervical, or unexplained infertility	245	1.09 (0.54-2.21)	TR	26	88	21	78	NS	3
Deaton et al.	Burlington USA 1990	Clomiphene plus IUI vs. timed coitus in natural cycle for unexplained infertility or surgically corrected endometriosis	51	3.20 (0.69-15.63)+	NS	8	15	4	24	NS	4
Gadir et al.	Kuwait City Kuwait 1990b	Ovarian electrocautery vs. hMG or FSH	88	0.71 (0.25-1.97)+*	TR	10	19	25	34	NS	6

		resistant polycystic ovary patients									
Hornstein et al.	Boston USA 1990	Comparison of two doses (1.25 mg vs. 2.5 mg) of gestrinone for endometriosis	12	0.20 (0.01-4.57)#	TR	0	4	2	2	NS	6
Johnson and Pearce	London UK 1990	Buserelin plus FSH vs. clomiphene for polycystic ovary syndrome with recurrent abortions	42	11.0 (1.68-91.7)	TR	18	2	9	11	USS-SAC	6

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; AIH, artificial insemination with husband's sperm; FSH, follicle-stimulating hormone.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes, one was added to all the groups);
*, more treatment groups were assigned in the trial, but they are combined here to make a 2 × 2 table.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; BIOCH, biochemical; USS-NS, ultrasound scan — not specified; USS-FH, ultrasound scan — fetal heart on scan; USS-SAC, ultrasound scan — gestational sac on scan.

Appendix 3A. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome on a Per Cycle Basis

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of treatment cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Casper et al.	Multicentre Canada 1983	hCG vs. placebo for luteal support in AID	? (74)	4.74 (1.00-23.83)	TR	12	27	3	32	USS-NS	1?
Hughes et al.	Ottawa Canada 1987	IUI vs. ICI for oligospermia	20 (63)	0.97 (0.02-37.4)#	TR	0	32	0	31	NS	3
Leeton et al.	Melbourne Australia 1987	GIFT vs. IVF for male infertility	14 (14)	1.00 (0.05-17.24)	PR	2	5	2	5	NS	1
Wikland et al.	Goteborg Sweden 1987	Self-migration method vs. swim-up for sperm preparation in IVF	80 (80)	4.61 (1.07-22.7)	NS	13	31	3	33	NS	1
Baerthlein et al.	Bethesda USA 1988	Simplified vs. complicated method of sperm preparation for AID	42 (201)	1.08 (0.37-3.17)	NS	8	85	10	98	USS-NS6	
Leong et al.	Happy Valley Hong Kong 1988	GIFT + IVF-ET vs. GIFT alone for male infertility	8 (8)	1.50 (0.03-81.25)#	PR	0	3	0	5	USS-FH1	

	1988	preparation methods in IVF										
Cohen et al.	Atlanta USA 1990b	Low-dose immunosuppression with methylprednisolone vs. no treatment in IVF with partial zona dissection for male infertility	37 (44)	8.27 (0.76-208.5)	PR	7	11	1	13	USS-FH	1-2
Federman et al.	Madison USA 1990	Urinary LH vs. BBT for timing of inseminations in AID	60 (264)	1.43 (0.13-15.7)+	NS	2	23	2	33	NS	1

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: hCG, human chorionic gonadotropin; AID, artificial insemination with donor sperm; IUI, intrauterine insemination; ICI, intracervical insemination; GIFT, gamete intrafallopian transfer; IVF, *in vitro* fertilization; DIPI, direct intraperitoneal insemination.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes, one was added to all the groups).

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; USS-NS, ultrasound scan — not specified; USS-FH, ultrasound scan — fetal heart on scan.

Appendix 3B. Randomized Trials for Female Infertility Treatment: Pregnancy Outcome on a Per Cycle Basis

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Trounson et al.	Melbourne Australia 1982	Early vs. delayed insemination of oocytes for IVF	90 (90)	0.22 (0.01-2.03)*#	NS	0	36	5	49	USS-NS	90
Huang et al.	Rochester USA 1984	Early vs. mid-follicular FSH for luteal-phase defect	15 (45)	1.12 (0.04-15.26)	NS	1	6	4	27	NS	45
Laufer et al.	New Haven USA 1984	Early vs. late hCG administration during controlled ovarian hyperstimulation in IVF	32 (32)	0.40 (0.01-6.85)	PR	1	16	2	13	NS	32
Quigley et al.	Houston USA 1984	Clomiphene plus hMG vs. clomiphene only for controlled ovarian hyperstimulation	32 (34)	1.00 (0.08-11.89)	TR	2	15	2	15	Clinical	34

et al.	USA 1984	hMG vs. clomiphene only for controlled ovarian hyperstimulation in IVF	(80)	98.7) #							
Yovich et al.	Perth Australia 1984	hCG vs. no luteal support in IVF (clomiphene with or without hMG cycles)	27 (27)	0.50 (0.05-4.33)	NS	3	14	3	7	USS-SAC	27
		Medroxyproges-terone acetate vs. no luteal support in IVF (clomiphene with or without hMG cycles)	27 (27)	0.71 (0.09-5.72)	NS	4	13	3	7	USS-SAC	27
Leeton et al.	Melbourne Australia 1985	Exogenous progestogen vs. no luteal support in IVF (clomiphene/ hMG cycles)	152 (152)	1.36 (0.54-3.46)	PR	14	58	12	68	BIOCH	152
Lewin et al.	Jerusalem Israel 1985	Ultrasonically guided percutaneous vs. laparoscopic ovum pick-up in IVF	20 (20)	1.00 (0.02-44.61)	NS	1	9	1	9	NS	20

Appendix 3B. *(cont'd)*

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
MacLennan et al.	Honolulu USA 1985	Relaxin vs. placebo for luteal support in IVF (controlled ovarian hyperstimulation not specified	96 (96)	0.85 (0.28-2.54)	TR	10	41	10	35	USS-NS	96
Mahadevan et al.	Calgary Canada 1985	hCG vs. no luteal support in IVF (clomiphene/ hMG cycles)	20 (20)	0.12 (0.01-1.63)#	PR	0	10	4	6	NS	20
O'Neill et al.	St. Leonards Australia 1985	hCG vs. no luteal support in IVF (controlled ovarian hyperstimulation not specified)	60 (60)	17.0 (2.03-374)#	NS	14	21	0	25	NS	60
Seibel et al.	Boston USA 1985	FSH vs. clomiphene-resistant polycystic ovary	23 (23)	0.30 (0.01-4.46)+	NS	1	10	3	9	NS	23

Bellinge et al.	Perth Australia 1986	vagina or not during ovum pick-up	(152)	8.98)								
Caro and Trounson	Melbourne Australia 1986	Comparison of two culture media for IVF (maternal serum vs. medium with no protein)	375 (375)	1.36 (0.75-2.47)	NS	36	161	25	153	NS	375
Cummins	Brisbane Australia 1986	Comparison of two culture media for IVF ("tubal fluid" vs. standard medium)	933 (933)	1.23 (0.84-1.80)	PR	77	406	60	390	USS-SAC	933
Englert et al.	Brussels Belgium 1986	Comparison of two methods of ET (knee-chest vs. dorsal position)	100 (100)	0.62 (0.21-1.79)	NS	9	36	14	35	BIOCH	100
Feichtinger et al.	Vienna Austria 1986	Comparison of two culture media for IVF (synthetic vs. patient serum)	90 (90)	1.00 (0.22-4.40)	NS	5	40	5	40	Clinical	90

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Kemeter and Feichtinger	Vienna Austria 1986	Addition of prednisolone or not during controlled ovarian hyperstimulation in IVF (clomiphene/ hMG or FSH cycles)	146 (146)	3.13 (1.06-9.68)	TR	16	57	6	67	BIOCH	146
Lewin et al.	Jerusalem Israel 1986	Ultrasonically guided transvaginal vs. laparoscopic ovum pick-up in IVF	120 (120)	1.16 (0.35-3.89)	NS	8	52	7	53	Clinical	120
Neveu et al.	Montpellier France 1986	Pulsatile subcutaneous vs. intra-muscular administration of FSH for controlled ovarian hyper-stimulation in	12 (12)	0.23 (0.01-4.27)#	NS	0	6	2	4	NS	12

	USA 1986	for controlled ovarian hyperstimulation in IVF	(36)	37.39)							
Sueldo and Swanson	San Francisco USA 1986	Pulsatile subcutaneous Gn-RH vs. intramuscular hMG for clomiphene-resistant anovulation	13 (13)	0.17 (0.01-2.89)#	NS	0	6	3	4	NS	13
Trounson et al.	Melbourne Australia 1986	Progesterone vs. no supplementation around ovum pick-up in IVF (clomiphene/ hMG cycles)	28 (28)	1.00 (0.14-6.84)	NS	4	10	4	10	NS	28
		hCG vs. no supplementation around ovum pick-up in IVF (clomiphene/ hMG cycles)	28 (28)	1.00 (0.14-6.84)	NS	4	10	4	10	NS	28
Abdalla et al.	London UK 1987	Low vs. high hCG dosage during controlled ovarian hyperstimulation in IVF	341 (341)	0.54 (0.17-1.53)*	NS	5	96	21	219	NS	341

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Belaisch-Allart et al.	Clamart France 1987	Dydrogesterone vs. placebo for luteal support in IVF	258 (258)	1.55 (0.78-3.09)	TR	27	98	20	113	NS	258
Dodson et al.	Durham USA 1987	Leuprolide plus hMG vs. hMG only for clomiphene-resistant polycystic ovary syndrome	13 (17)	3.50 (0.20-115.9)	NS	3	6	1	7	NS	17
Fishel et al.	Nottingham UK 1987	Halothane vs. enflurane general anaesthetic for ET in IVF	226 (226)	0.38 (0.18-0.77)	PR	15	72	49	90	USS-SAC	226
Imoedemhe et al.	London UK 1987	Comparison of two clomiphene/hMG protocols for controlled ovarian hyperstimulation in IVF	64 (107)	0.27 (0.04-1.42)	NS	2	35	12	58	USS-SAC	107

	Australia 1987	unexplained infertility	(86)	3.69)							
Lehtinen et al.	Helsinki Finland 1987	Epidural vs. general anaesthetic for laparoscopic ovum pick-up in IVF	24 (24)	1.16 (0.02-48.9)#	NS	0	11	0	13	NS	24
Mahadevan et al.	Calgary Canada 1987	Day 2 vs. day 4 initiation of controlled ovarian hyperstimulation in IVF (clomiphene/ hMG cycles)	104 (104)	1.15 (0.36-3.66)	NS	9	43	8	44	BIOCH	104
Mavroudis et al.	Salford UK 1987	Intramuscular progesterone vs. placebo for luteal-phase defect	24 (31)	0.94 (0.02-38.30)+#	TR	0	16	0	15	BIOCH	31
Messinis and Templeton	Aberdeen UK 1987	Pulsatile FSH vs. late follicular exogenous estradiol for unexplained infertility	10 (10)	1.00 (0.02-49.39)#	NS	0	5	0	5	NS	10

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Neveu et al.	Montpellier France 1987	Buserelin plus FSH vs. FSH only for controlled ovarian hyperstimulation in IVF	20 (20)	13.5 (0.92-4.64)	NS	6	4	1	9	NS	20
Parinaud et al.	Toulouse France 1987a	Clomiphene plus hMG vs. hMG only for controlled ovarian hyperstimulation in IVF	126 (126)	2.68 (0.71-10.89)	NS	10	54	4	58	USS-NS	126
Parinaud et al.	Toulouse France 1987b	Comparison of two culture media for IVF (Ham's F10 vs. Menezo B2)	76 (76)	1.20 (0.31-4.64)	NS	7	31	6	32	NS	76
Scoccia et al.	Chicago USA 1987	FSH vs. hMG for controlled ovarian hyperstimulation	48 (63)	2.85 (0.34-27.06)	NS	3	20	2	38	BIOCH	63

Shaw et al.	UK 1987	pulsatile subcutaneous LH-RH with or without clomiphene for controlled ovarian hyperstimulation in IVF	(16)	44.6)#							
Torode et al.	Sydney Australia 1987	hCG vs. no luteal support in IVF (clomiphene/ hMG cycles)	236 (236)	1.23 (0.49-3.09)	NS	14	46	14	57	NS	236
Baber et al.	St. Leonards Australia 1988	Early pregnancy support with hCG or not following IVF (clomiphene/ hMG or FSH cycles)	60 (60)	1.00 (0.27-3.63)	NS	22	8	22	8	USS-NS	60
Benadiva et al.	Philadelphia USA 1988	Combined FSH/hMG vs. hMG only for controlled ovarian hyperstimulation in IVF	110 (110)	1.40 (0.36-5.52)	TR	7	49	5	49	NS	110

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Buvat et al.	Lille France 1988	hCG vs. no luteal support in IVF (hMG with or without clomiphene cycles)	116 (116)	1.05 (0.33-3.32)	PR	9	51	8	48	USS-SAC	116
Frydman et al.	Clamart France 1988a	Long vs. short Gn-RHa plus hMG protocol for controlled ovarian hyperstimulation in IVF	186 (186)	1.68 (0.79-3.57)	NS	26	68	17	75	NS	186
Janssen-Caspers et al.	Rotterdam Netherlands 1988	Transvaginal vs. percutaneous ultrasonically guided ovum pick-up in IVF	47 (47)	3.06 (0.57-18.07)	NS	7	16	3	21	NS	47
Lavy et al.	New Haven USA 1988	FSH vs. hMG for controlled ovarian hyperstimulation	40 (40)	2.11 (0.13-64.78)	NS	2	18	1	19	USS-SAC40	

Leong et al.	1988	IVF-ET vs. GIFT alone for unexplained infertility	(20)	1.98)							
Nader et al.	Houston USA 1988	Intramuscular progesterone vs. hCG for luteal support in IVF (clomiphene/ hMG cycles)	17 (20)	0.25 (0.01-3.19)#	NS	0	10	3	7	Clinical	20
Quigley et al.	Cleveland USA 1988	Clomiphene plus FSH vs. clomiphene plus hMG for controlled ovarian hyperstimulation in IVF	98 (98)	0.77 (0.18-3.17)	TR	5	45	6	42	USS-NS	98
Salat-Baroux et al.	Paris France 1988a	Gn-RHa plus FSH vs. FSH only for controlled ovarian hyperstimulation in IVF (polycystic ovary syndrome patients)	16 (17)	0.41 (0.03-4.83)	NS	5	6	4	2	NS	17

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Salat-Baroux et al.	Paris France 1988b	Long vs. short Gn-RHa plus FSH protocol for controlled ovarian hyperstimulation in IVF (polycystic ovary syndrome patients)	27 (27)	1.20 (0.19-8.10)	NS	15	9	3	9	NS	27
Salat-Baroux et al.	Paris France 1988c	Programmed vs. classical monitoring during controlled ovarian hyperstimulation in IVF	84 (84)	0.33 (0.07-1.32)	NS	4	38	10	32	NS	84
		FSH plus hMG vs. clomiphene plus hMG for controlled ovarian hyperstimulation in IVF	84 (84)	1.00 (0.27-3.61)	NS	7	35	7	35	NS	84

Van der Ven et al.	Bonn Germany 1988b	General anaesthetic vs. no general anaesthetic for ET	(215)	4.14)							
Van Steirteghem et al.	Brussels Belgium 1988	Intramuscular progesterone vs. no luteal support in IVF/GIFT (clomiphene/ hMG cycles)	68 (168)	1.53 (0.69-3.41)	NS	18	50	19	81	NS	168
Van Steirteghem et al.	Brussels Belgium 1988	Intramuscular progesterone plus oral estradiol vs. hCG for luteal support in IVF/GIFT (Gn-RHa/hMG cycles)	91 (91)	1.01 (0.38-2.70)	NS	16	34	13	28	NS	91
Ashkenazi et al.	Petha Tikva Israel 1989	Gn-RHa plus FSH/hMG vs. FSH with or without hMG only for controlled ovarian hyperstimulation in IVF	18 (18)	3.00 (0.25-41.07)*	NS	3	3	3	9	NS	18

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Benadiva et al.	Philadelphia USA 1989	Comparison of two culture media for IVF (bovine serum albumin vs. patient's serum)	127 (127)	1.32 (0.47-3.70)	PR	11	40	11	53	NS	127
Brinsmead et al.	Newcastle Australia 1989	Ultrasonically guided transvaginal vs. laparoscopic ovum pick-up in IVF	94 (166)	1.08 (0.37-3.22)	NS	14	50	8	31	BIOCH	166
Caspi et al.	Zerifin Israel 1989	Two-stage vs. one-stage ET in IVF	51 (51)	0.70 (0.19-2.63)*	NS	8	9	19	15	NS	51
Chang et al.	Taipei Taiwan 1989	Immediate vs. delayed intramuscular progesterone for luteal support in GIFT	76 (86)	0.81 (0.26-2.49)	PR	9	33	11	33	USS-SAC	86
Dodson et al.	Durham USA 1989	Leuprolide plus hMG vs. hMG only for	27 (58)	1.97 (0.45-9.03)	NS	9	24	4	21	NS	58

		ovarian hyperstimulation in IVF									
Gianaroli et al.	Multicentre International 1989	Comparison of two culture media for IVF (human amniotic fluid vs. Whittingham's medium)	716 (716)	1.26 (0.80-1.98)	PR	40	195	67	414	USS-SAC	716
Gianaroli et al.	Clayton Australia 1989	Comparison of two culture media for IVF (human amniotic fluid vs. Whittingham's medium)	780 (780)	0.91 (0.59-1.39)	PR	43	258	74	405	USS-SAC	780
Khan et al.	Brussels Belgium 1989a	100% CO_2 vs. 5% CO_2 pneumoperitoneum during laparoscopic ovum pick-up in IVF or GIFT	246 (246)	1.36 (0.71-2.60)	NS	31	93	24	98	NS	246
Khan et al.	Brussels Belgium 1989b	Early vs. delayed insemination of oocytes for IVF	151 (151)	0.44 (0.17-1.09)*	NS	9	48	28	66	NS	151
Lewin et al.	Jerusalem Israel 1989	Two-stage vs. one-stage ET in IVF	67 (67)	2.15 (0.60-7.85)	NS	11	23	6	27	NS	67

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Lipitz et al.	Tel-Hashomer Israel 1989	Gn-RHa plus hMG/FSH vs. hMG/FSH only for controlled ovarian hyperstimulation in IVF	78 (78)	5.08 (0.60-111.6)*	NS	13	46	1	18	NS	78
Loumaye et al.	Brussels Belgium 1989	Long vs. short Gn-RHa plus hMG protocol for controlled ovarian hyperstimulation in IVF	18 (18)	2.28 (0.11-81.26)	NS	2	7	1	8	NS	18
Marconi et al.	Buenos Aires Argentina 1989	Coitus vs. abstinence during GIFT	37 (37)	9.53 (1.47-72.25)	PR	13	3	5	11	USS-NS	37
McFaul et al.	Belfast UK 1989b	Daily vs. alternate-day FSH for clomiphene-resistant polycystic ovary syndrome	12 (39)	0.38 (0.06-2.23)	NS	3	17	6	13	NS	39

Menezo et al.	Multicentre International 1989	High vs. normal viscosity transfer medium for ET in IVF	(787)	1.41)							
Mitchell et al.	Bristol UK 1989	Full vs. empty bladder during ET in IVF	142 (142)	1.07 (0.41-2.77)	TR	12	54	13	63	USS-NS	142
O'Neill et al.	Sydney Australia 1989	Comparison of two culture media for IVF (supplemented with platelet activating factor or not)	351 (351)	1.85 (0.95-3.60)*	PR	29	137	19	166	BIOCH	351
Pellicer et al.	Valencia Spain 1989a	Luteal- vs. follicular-phase initiation of Gn-RHa prior to controlled ovarian hyperstimulation in IVF	44 (44)	0.24 (0.04-1.28)*	NS	4	25	6	9	USS-FH	44
Psalti et al.	Brussels Belgium 1989	Comparison of two culture media for IVF (serum substitute vs. fetal cord serum)	141 (141)	0.33 (0.11-0.97)	PR	6	61	17	57	NS	141

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Rabinowitz et al.	Jerusalem Israel 1989	"Step-up" vs. "step-down" hMG/hCG protocol for controlled ovarian hyperstimulation in IVF	58 (58)	1.41 (0.28-7.30)	NS	5	23	4	26	USS-SAC	58
Remorgida et al.	Genova Italy 1989	Long vs. short Gn-RHa plus FSH/hMG protocol for controlled ovarian hyperstimulation in IVF	178 (178)	1.08 (0.54-2.15)	NS	31	65	25	57	NS	178
Smith et al.	Southampton UK 1989	hCG vs. no luteal support in IVF (Gn-RHa/hMG cycles)	115 (115)	3.99 (1.48-10.99)	PR	25	36	8	46	USS-SAC	115

Sopelak et al.	Jackson USA 1989	Bromocriptine not prior to ovum pick-up in IVF for anaesthesia-induced hyperprolactinemia	(32)	8.08)*								
van Os et al.	Rotterdam Netherlands 1989	Day 3 ET vs. day 2 ET in IVF	581 (758)	2.06 (1.38-3.08)	PR	67	181	66	368	BIOCH	758	
Wu and Winkel	Philadelphia USA 1989	Early (day 2 to 3) vs. late (day 4 to 5) initiation of clomiphene for anovulation	87 (414)	0.63 (0.26-1.49)*	NS	10	187	17	200	NS	414	
Abdalla et al.	London UK 1990	Gn-RHa plus hMG vs. clomiphene plus hMG for controlled ovarian hyperstimulation in IVF/GIFT	220 (220)	2.44 (1.16-5.17)	PR	33	85	14	88	USS-SAC220		
Aboulghar et al.	Cairo Egypt 1990	Aspiration of pelvic inflammatory cystic masses or not before controlled ovarian hyperstimulation in IVF	64 (64)	1.79 (0.32-10.65)	PR	5	27	3	29	NS	64	

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Antoine et al.	Paris France 1990	Gn-RHa plus hMG vs. hMG only for controlled ovarian hyperstimulation in IVF	180 (180)	1.92 (0.80-4.66)	NS	19	71	11	79	NS	180
Bachus et al.	Durham USA 1990	Gn-RHa plus hMG vs. hMG only for clomiphene-resistant polycystic ovary syndrome	28 (59)	1.57 (0.39-6.51)	NS	9	24	5	21	BIOCH	59
Barash et al.	Tel-Hashomer Israel 1990	Aspiration of an ill-timed leading follicle or not during controlled ovarian hyperstimulation for IVF	12 (12)	3.00 (0.16-101.3)#	TR	2	5	0	5	NS	12

Belaisch-Allart et al.	Multicentre France 1990a	for luteal support in IVF (Gn-RHa/ hMG cycles)	(387)	2.41)							
Belaisch-Allart et al.	Multicentre France 1990b	Comparison of two regimens (single vs. double injection) of subcutaneous buserelin for downregulation prior to controlled ovarian hyperstimulation in IVF	96 (96)	1.45 (0.55-3.86)	TR	17	33	12	34	NS	96
Buvat et al.	Lille France 1990	hCG vs. oral progesterone for luteal support in IVF (Gn-RHa/ hMG cycles)	140 (140)	2.75 (1.10-6.93)	PR	22	48	10	60	USS-SAC	140
Cohen et al.	Atlanta USA 1990a	Assisted hatching or not to improve implantation in IVF	79 (79)	0.50 (0.17-1.48)	PR	9	30	15	25	Clinical	79
Daures et al.	Montpellier France 1990	Early vs. late monitoring of controlled ovarian hyperstimulation in IVF (Gn-RHa/ hMG cycles)	122 (122)	1.05 (0.41-2.65)	TR	15	38	15	40	USS-SAC	122

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Edelstein et al.	Norfolk USA 1990	Gn-RHa plus FSH vs. Gn-RHa plus hMG for controlled ovarian hyperstimulation in IVF	37 (37)	1.16 (0.24-5.57)	PR	7	12	6	12	Clinical	37
Fakih and Vijayakumar	Saginaw USA 1990	Comparison of two culture media for GIFT (follicular fluid vs. Ham's F10)	58 (58)	5.43 (1.48-20.79)	NS	17	12	6	23	NS	58
Feldberg et al.	Petah Tikva Israel 1990	Decapeptyl vs. buserelin for downregulation prior to controlled ovarian hyperstimulation in IVF	91 (91)	1.45 (0.56-3.76)	NS	19	28	14	30	USS-FH	91
Ferrier et al.	New York USA 1990	Gn-RHa plus hMG vs. clomiphene plus	76 (93)	0.50 (0.09-2.31)	NS	3	35	8	47	USS-FH	93

		ovarian hyperstimulation in IVF/GIFT									
Garcia et al.	Baltimore USA 1990	Luteal- vs. follicular-phase initiation of Gn-RHa prior to controlled ovarian hyperstimulation for IVF	195 (195)	0.66 (0.34-1.28)	NS	25	70	35	65	USS-NS	195
Gindoff et al.	Washington USA 1990	Luteal- vs. follicular-phase initiation of Gn-RHa prior to controlled ovarian hyperstimulation for IVF	62 (62)	0.93 (0.24-3.59)	PR	9	29	6	18	USS-FH	62
		Comparison of two maintenance dosages of Gn-RHa following downregulation during controlled ovarian hyperstimulation in IVF	62 (62)	1.64 (0.39-7.05)	PR	7	23	5	27	USS-FH	62

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Gonen et al.	Toronto Canada 1990	Mid-cycle Gn-RHa vs. hCG to trigger follicular maturation during controlled ovarian hyperstimulation in IVF	14 (18)	5.70 (0.40-168.0)#	TR	3	6	0	9	NS	18
Herman et al.	Zerifin Israel 1990	hCG vs. no luteal support in IVF (Gn-RHa/hMG cycles)	36 (36)	5.00 (0.87-31.93)	NS	9	9	3	15	USS-NS	36
Homburg et al.	London UK 1990c	Gn-RHa plus FSH/hMG vs. FSH/hMG for clomiphene-resistant polycystic ovary syndrome	42 (122)	0.94 (0.23-3.77)*	NS	5	52	6	59	NS	122
		FSH with or without Gn-RHa vs. hMG with or without Gn-RHa	46 (122)	1.82 (0.45-7.45)*	NS	6	44	5	67	NS	122

		polycystic ovary syndrome									
Homburg et al.	London UK 1990a	hMG plus growth hormone vs. hMG plus placebo for anovulation	16 (16)	2.33 (0.11-86.3)+	TR	2	6	1	7	NS	16
Kubik et al.	Pittsburg USA 1990	Gn-RHa plus hMG vs. clomiphene plus hMG for controlled ovarian hyperstimulation in IVF/GIFT	114 (114)	1.96 (0.80-4.79)	NS	23	37	13	41	BIOCH	114
Kupferminc et al.	Tel Aviv Israel 1990	hCG vs. placebo for luteal support in IVF (hMG cycles)	102 (102)	1.22 (0.46-3.29)	NS	14	37	12	39	Clinical	102
		Dydrogesterone vs. placebo for luteal support in IVF (hMG cycles)	105 (105)	1.36 (0.52-3.58)	NS	16	38	12	39	Clinical	105
Leyendecker et al.	Darmstadt Germany 1990	Gn-RHa plus hMG vs. hMG only for controlled ovarian hyperstimulation in IVF	? (453)	2.60 (1.44-4.73)	NS	49	186	20	198	NS	453

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Mansour et al.	Cairo Egypt 1990	Dummy ET or not prior to IVF	335 (335)	1.95 (1.05-3.62)	PR	38	129	22	146	NS	335
McFaul et al.	Belfast UK 1990	FSH vs. hMG for clomiphene-resistant polycystic ovary syndrome	49 (179)	1.13 (0.32-4.31)*	NS	15	123	4	37	USS-SAC	179
Quinn et al.	Los Angeles USA 1990	Day 1 ET vs. day 2 ET in IVF	174 (174)	1.48 (0.59-3.72)	NS	14	65	12	83	NS	174
Rizk et al.	London UK 1990	Aspiration or not of pre-existing cysts prior to controlled ovarian hyperstimulation in IVF	14 (14)	1.40 (0.02-70.3)	NS	1	5	1	7	NS	14

	UK 1990	of cysts developing during controlled ovarian hyperstimulation in IVF	(23)	39.4)							
Ron-El et al.	Zerefin Israel 1990	Luteal- vs. follicular-phase initiation of Gn-RHa prior to controlled ovarian hyperstimulation in IVF	216 (216)	0.78 (0.40-1.51)	NS	24	84	29	79	Clinical	216
Staessen et al.	Brussels Belgium 1990	Comparison of two culture media in IVF/GIFT (Albuminar-20 [TM] vs. human semen)	286 (286)	1.64 (0.93-2.91)	PR	42	94	32	118	NS	286
Tanbo et al.	Oslo Norway 1990b	Gn-RHa plus hMG vs. hMG with or without clomiphene for controlled ovarian hyperstimulation in IVF	43 (70)	4.66 (0.44-115.9)*	NS	4	30	1	35	NS	70

Appendix 3B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	No. of randomized cycles
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Tanbo et al.	Oslo Norway 1990c	Gn-RHa plus FSH vs. Gn-RHa plus hMG for controlled ovarian hyperstimulation in IVF (for clomiphene - resistant polycystic ovary syndrome)	34 (34)	1.80 (0.29-11.44)	NS	5	9	4	13	Clinical	34
Thornton et al.	Carlton Australia 1990	Delayed vs. earlier ovum pick-up in IVF (clomiphene/ hMG cycles)	214 (214)	0.96 (0.46-2.00)	PR	20	86	21	87	NS	214
Van de-Helder et al.	Leiden Netherlands 1990	Long vs. short Gn-RHa plus hMG protocol for controlled ovarian hyperstimulation	101 (101)	0.58 (0.20-1.64)	NS	9	41	14	37	USS-FH	101

		hMG vs. hMG only for controlled ovarian hyperstimulation in IVF	(153)	3.98)								
Wong et al.	Hong Kong 1990	Progesterone vs. no luteal support in IVF (clomiphene/ hMG cycles)	20 (20)	2.25 (0.11-77.60)	NS	2	8	1	9	NS	20
Wong et al.	Hong Kong 1990	Progesterone plus hCG vs. no luteal support in IVF (clomiphene/ hMG cycles)	20 (20)	3.85 (0.24-121.5)	NS	3	7	1	9	NS	20

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: IVF, *in vitro* fertilization, FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; ET, embryo tranfer; Gn-RHa, gonadotropin-releasing hormone agonist; GIFT, gamete intrafallopian transfer; LH-RH, luteinizing hormone-releasing hormone.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes, one was added to all the groups);
*, more treatment groups were assigned in the trial, but they are combined here to make a 2 × 2 table.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; BIOCH, biochemical; USS-NS, ultrasound scan — not specified; USS-FH, ultrasound scan — fetal heart on scan; USS-SAC, ultrasound scan — gestational sac on scan.

Appendix 4A. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome — Remaining Trials

Author	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Berger and Taymor	Boston USA 1971	hMG vs. placebo for ovarian stimulation and timing of insemination in AID	20	CO	NS
Wieland et al.	Cleveland USA 1972	Cisclomiphene vs. placebo for oligospermia	11	CO ID	NS
Friberg and Gemzell	Uppsala Sweden 1973	Comparison of two methods of sperm cryopreservation for AID	83	CO	NS
Steinberger and Smith	Houston USA 1973	Fresh vs. frozen semen for AID	74	CO	NS
Schill and Littich	Munich Germany 1981	Addition of kallikrein to split ejaculates in AIH for oligospermia	48	CO ID	TR
Luisi et al.	Pisa Italy 1982	Levamisole vs. placebo for male immunological infertility	25	CO ID	TR
Wang et al.	Hong Kong 1983	Comparison of placebo, clomiphene, mesterolone, pentoxifylline, and testosterone for oligospermia	46	CO MCG	NS
Kerin et al.	Woodville Australia 1984	IUI vs. coitus for oligospermia	35	CO	NS

	USA 1984				
Francavilla et al.	L'Aquilla Italy 1985	IUI vs. coitus for negative post-coital test	26	CO	NS
Cruz et al.	New Brunswick USA 1986	IUI vs. ICI (combined with ovulation induction) for oligospermia	49	CO	NS
Irvine et al.	Edinburgh UK 1986	IUI vs. ICI for unexplained infertility	21	CO	NS
AinMelk et al.	Sherbrooke Canada 1987	Tamoxifen vs. placebo for oligospermia	16	CO ID	NS
Glazener et al.	Bristol UK 1987b	IUI vs. coitus for negative post-coital test	46	CO	PR
Brown et al.	Madison USA 1988	Fresh vs. frozen semen (using a new cryopreservation method) for AID	288	CO	NS
Micic et al.	Belgrade Yugoslavia 1988	Pentoxifylline vs. observation for oligospermia	90	ID	NS
Blumenfeld and Nahhas	Haifa Israel 1989	Follicular fluid vs. placebo-treated sperm in IUI for oligospermia	31	CO	NS
Claraz et al.	Lyon France 1989	hCG or not for ovulation and timing of insemination in AID	77	ID	NS

Appendix 4A. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Clark and Sherins	Atlanta USA 1989	Testolactone vs. placebo for oligospermia	33	CO	TR
Friedman et al.	Boston USA 1989	IUI vs. ICI for oligospermia	19	CO	NS
Ho et al.	Hong Kong 1989	IUI vs. coitus for oligospermia	47	CO	PR
Remohi et al.	Orange USA 1989	Percoll gradient vs. swim-up for sperm preparation in IUI	186	ID	NS
te Velde et al.	Utrecht Netherlands 1989	IUI vs. coitus for oligospermia	30	CO	NS
Byrd et al.	Dallas USA 1990	IUI vs. ICI of cryopreserved sperm for AID	154	CO	TR
Comhaire	Ghent Belgium 1990	Testosterone vs. placebo for oligospermia	25	CO	TR
Gerhard et al.	Heidelberg Germany 1990	Comparison of native, washed, or kallikrein-treated semen for AIH vs. coitus	172	MCG	NS

Henury et al.	Manchester UK 1990	infertility			
Martinez et al.	Amsterdam Netherlands 1990	Clomiphene vs. spontaneous cycles and IUI vs. coitus in 4 combinations	40	CO MCG	NS
Patton et al.	Portland USA 1990	IUI vs. ICI for AID with donor sperm	26	CO	NS

Notes: Incomplete data; crossover trial design with insufficient data.

Evaluation: hMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; AID, artificial insemination with donor sperm; AIH, artificial insemination with husband's sperm; IUI, intrauterine insemination; ICI, intracervical insemination.

Trial problem: MCG, multiple comparison groups (more than two); ID, insufficient data; CO, crossover.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Appendix 4B. Randomized Trials for Female Infertility Treatment: Pregnancy Outcome — Remaining Trials

Author	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Starup and Sele	Copenhagen Denmark 1972	Comparison of three dosages of hCG for anovulation (hMG/hCG cycles)	44	MCG	NS
Connaughton et al.	Philadelphia USA 1974	Cisclomiphene vs. placebo for anovulation	19	CO ID	TR
Soihet	Lima Peru 1974	Comparison of three techniques of tuboplasty	258	ID MCG	NS
Benedek-Jaszmann and Hearn-Sturtevant	Bennekom Netherlands 1976	Bromocriptine vs. placebo for premenstrual tension (in infertility patients)	17	CO ID	TR
Hinton et al.	Bristol UK 1979	Doxycycline vs. placebo for unexplained infertility	42	CO ID	TR
Annos et al.	Boston USA 1980	Vaginal progesterone vs. clomiphene vs. no treatment for luteal-phase defect	14	CO ID	NS
Sutaria et al.	Birmingham UK 1980	Comparison of two dosages of clomiphene and hCG or not for anovulation	51	CO MCG	TR

et al.	Sweden 1981	defect		ID	
McBain and Pepperell	Parkville Australia 1982	Bromocriptine vs. placebo for unexplained infertility	50	CO ID	TR
Daly et al.	Farmington USA 1984	Clomiphene plus dexamethasone vs. clomiphene only for anovulation	64	CO	TR
Elstein and Fawcett	Manchester UK 1984	Clomiphene (two dosages) vs. tamoxifen (two dosages) vs. no treatment for anovulation	40	CO	TR
Porter et al.	London UK 1984	Gn-RHa plus FSH vs. Gn-RHa plus hMG for controlled ovarian hyperstimulation in IVF	11	ID	NS
Hoffman et al.	Los Angeles USA 1985	FSH vs. hMG for clomiphene-resistant anovulation	15	CO	NS
Larsson et al.	Multicentre Sweden 1985	Intraperitoneal instillation of Dextran vs. saline following tubal surgery	109	ID	TR
Tal et al.	Haifa Israel 1985	Clomiphene plus hMG vs. hMG only for clomiphene-resistant anovulation	46	CO	NS
Archer et al.	Pittsburgh USA 1986	Intermittent subcutaneous hMG vs. daily intramuscular hMG for ovulatory dysfunction	20	CO	TR

Appendix 4B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Buvat et al.	Lille France 1987	Clomiphene vs. tamoxifen for anovulation	26	CO ID	NS
Buvat et al.	Lille France 1987	Clomiphene vs. tamoxifen for luteal-phase defect	40	CO ID	NS
Coutinho et al.	Salvador Bahia Brazil 1987	Vaginal vs. oral gestrinone for endometriosis	100	MCG ID	NS
Glazener et al.	Bristol UK 1987a	Bromocriptine vs. placebo for unexplained infertility (with borderline hyperprolactinemia)	22	CO	TR
Bentick et al.	London UK 1988	Gn-RHa plus FSH vs. Gn-RHa plus hMG for controlled ovarian hyperstimulation in IVF	20	CO ID	NS
Blumenfeld and Nahhas	Haifa Israel 1988	hCG vs. no luteal-phase support in ovulation induction (clomiphene or hMG cycles)	74	CO	PR
Harrison	Dublin Ireland 1988	Clomiphene plus bromocriptine vs. placebo for unexplained infertility	70	CO ID	NS
Pampiglione et al.	London UK 1988	Day 2 vs. day 4 initiation of hMG for controlled ovarian hyperstimulation in IVF (clomiphene/hMG cycles)	170	ID	NS
Buvat et al.	Lille France	Slow vs. conventional FSH administration for clomiphene-resistant polycystic ovary syndrome	11	CO ID	NS

Fisch et al.	Tel Aviv Israel 1989b	after ovum pick-up in IVF	(cycles)	ID	
Friedman et al.	Boston USA 1989	IUI vs. ICI for cervical infertility	54	CO	NS
Mashiach et al.	Tel-Hashomer Israel 1989	15-day vs. 30-day administration of oral contraceptive pill for downregulation prior to controlled ovarian hyperstimulation in IVF	61	ID	NS
McFaul et al.	Belfast UK 1989a	FSH (three protocols) vs. hMG for clomiphene-resistant polycystic ovary syndrome	49	ID	NS
Quartero et al.	London UK 1989	Intramuscular vs. pulsatile subcutaneous FSH for clomiphene-resistant polycystic ovary syndrome	12	CO	TR
Sharma et al.	London UK 1989	Comparison of six regimens for controlled ovarian hyperstimulation in IVF	91	MCG	NS
te Velde et al.	Utrecht Netherlands 1989	IUI vs. coitus for cervical mucus hostility	27	CO	NS
Wisanto et al.	Brussels Belgium 1989	Comparison of three ET catheters	400	MCG	TR
Everhardt et al.	Nijmegen Netherlands 1990	Vaginal douching with sodium bicarbonate vs. sodium chloride for negative post-coital test	25	CO ID	TR

Appendix 4B. (*cont'd*)

Author	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Glazener et al.	Bristol UK 1990	Clomiphene vs. placebo for unexplained infertility	118	CO	TR
Homburg et al.	London UK 1990b	Gn-RHa plus hMG vs. hMG only for clomiphene- resistant polycystic ovary syndrome	8	CO ID	NS
Larsen et al.	Copenhagen Denmark 1990	FSH vs. hMG for clomiphene-resistant polycystic ovary syndrome	12	CO	TR
Martinez et al.	Amsterdam Netherlands 1990	Clomiphene or spontaneous cycle and IUI or coitus (four combinations) for unexplained infertility	21	CO MCG	NS
Tanbo et al.	Oslo Norway 1990a	Tubal embryo-stage transfer vs. GIFT vs. IVF for infertility with patent tubes	150	MCG	NS

Notes: Incomplete data — crossover trial design with insufficient data.

Evaluation: hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; Gn-RHa, gonadotropin-releasing hormone agonist; FSH, follicle-stimulating hormone; IVF, *in vitro* fertilization; IUI, intrauterine insemination; ICI, intracervical insemination; ET, embryo transfer; GIFT, gamete intrafallopian transfer.

Trial problem: CO, crossover; MCG, multiple comparison groups (more than two); ID, insufficient data.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

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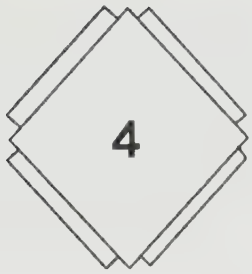
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Meta-Analysis of Controlled Trials in Infertility

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Executive Summary

Meta-analysis (or quantitative overview analysis) provides the tools with which a greater level of agreement may be reached in answering important clinical questions and identifying areas of ignorance. This approach involves (1) development of a specific question, including a clear description of the population involved, the intervention used, and the outcome measured (e.g., in couples with unexplained infertility, does the use of clomiphene citrate [CC] improve the rate of ongoing clinical pregnancy?); (2) identification of relevant studies; (3) assessment of study validity; and (4) extraction and appropriate pooling of data.

In this paper the authors summarize the results of meta-analyses of articles describing clinically controlled trials for unexplained infertility, endometriosis-related infertility, and assisted reproductive technology, including their risks and costs.

Part 1. Controlled Trials in Unexplained Infertility

The treatments (interventions) assessed in this section were bromocriptine, Danazol®, superovulation with clomiphene, intrauterine insemination (IUI), superovulation with human menopausal gonadotropin (hMG) ± IUI, and *in vitro* fertilization (IVF) versus gamete intrafallopian transfer (GIFT).

This paper was completed for the Royal Commission on New Reproductive Technologies in May 1992.

Bromocriptine

There seems to be no apparent benefit from bromocriptine use in women with unexplained infertility. However, one cohort study did report a higher conception rate in these women when treated with bromocriptine compared with pyridoxine. As the women in the control group were older, had a longer period of infertility, and had lower basal prolactin levels, the validity of this conclusion is highly questionable. Larger trials for specific subgroups, e.g., normoprolactinemic women with unexplained infertility and galactorrhoea, may be warranted.

Danazol®

Given in a low dose, Danazol® does not appear to improve the outcome in unexplained infertility. In addition, contraception must be used during treatment because of the risk of virilization of the fetus, thus eliminating the chance of spontaneous pregnancy. The cost of this treatment and its side-effects, which include weight gain, oily skin, and, rarely, hirsutism and clitoromegaly, are important concerns.

Clomiphene Citrate

The risk of multiple pregnancy is increased with clomiphene use (to approximately 10%), and ovarian cyst formation may occur. Although no increases in spontaneous abortion or fetal abnormality have been demonstrated, women should be counselled to avoid clomiphene following an abnormal or missed period in order to reduce the risk of fetal exposure. Although the data support the use of clomiphene in patients with unexplained infertility, the strength of this conclusion is not great because of the inconsistent quality of the trials. Large, randomized controlled trials of parallel design are warranted to assess this intervention further and to address the questions of optimal dose and responses in different patient subgroups. Clomiphene should be used as a primary treatment in this patient group because it is easy to administer, has a relatively low cost, and has a low incidence of side-effects. It may be more effective in women who have been infertile for more than three years.

Intrauterine Insemination

Neither of the studies analyzed demonstrated significant benefit from IUI in couples with unexplained infertility. Because of the limited power and quality of the data, this conclusion is weak. A cohort study suggested significant benefit in women with infertility caused by a cervical mucus factor. Additional trials are warranted to address the effectiveness of IUI in unexplained and other types of infertility.

Human Menopausal Gonadotropin With or Without Intrauterine Insemination

There appears to be some benefit from hMG plus IUI versus hMG plus intercourse in couples with unexplained infertility. However, the data from studies comparing these two interventions are heterogeneous and of poor quality. This is an important area for further study — small treatment benefits may exist, but at the potential cost of significant side-effects, for example, ovarian hyperstimulation and multiple pregnancy.

In Vitro Fertilization Versus Gamete Intrafallopian Transfer

No significant difference has been demonstrated between IVF and GIFT in the treatment of unexplained infertility. However, the power of the small, randomized controlled trials available was insufficient to demonstrate clinically significant differences. Although cohort studies suggest that GIFT may be superior in this patient group, their validity is questionable.

Summary

There is no sound evidence to support the use of bromocriptine, Danazol®, or IUI in the treatment of unexplained infertility. Available evidence suggests a significant treatment benefit from CC. Based upon its relatively low cost and limited risks, it should be used as a primary therapy in couples requesting treatment. Although hMG plus IUI may have a positive treatment effect, this approach is relatively expensive and carries significant risks of multiple pregnancy and ovarian hyperstimulation. Well-designed trials of this intervention are warranted, since the quality of the available data is low. Although data from cohort studies suggest that GIFT is superior to IVF in the treatment of unexplained infertility, randomized controlled trials have demonstrated no significant difference between the two interventions. This may be a genuine finding or a function of limited statistical power.

Part 2. Controlled Trials in Endometriosis-Related Infertility

Part 2 reports on studies dealing with the use of ovulation suppression, laparoscopic surgery, the combination of laparoscopic surgery and Danazol®, conservative laparotomy, and the combination of conservative laparotomy and Danazol® in the treatment of endometriosis-related infertility. As Danazol® has long been the treatment of choice for this condition, and its efficacy has been found to be similar to that of placebo or no treatment at all, in some overviews data from studies including Danazol® as an "active control" have been combined with those from placebo or no-treatment control groups.

Ovulation Suppression

This term is used to describe all agents that impair ovarian steroidogenesis. It was found that ovulation suppression agents do not improve the pregnancy rate of women suffering from endometriosis-associated infertility. Furthermore, based on these findings, larger trials do not appear to be warranted.

Laparoscopic Surgery

Data pooled from five studies demonstrated significant benefit of laparoscopic destruction of endometriotic implants. However, because of the significant heterogeneity among the studies analyzed, this conclusion cannot be made with confidence. The apparent beneficial effect of this treatment deserves further study in large, well-controlled randomized trials.

Combination of Laparoscopic Surgery and Danazol®

There is no evidence to support the use of adjuvant Danazol® with laparoscopic surgery in the infertility-directed treatment of endometriosis. However, the methodological quality of existing evidence is poor. The assessment of laparoscopic ablation alone should remain the priority of further study, given the discouraging results of ovulation suppression for this condition.

Conservative Laparotomy

Existing evidence does not support the use of this intervention in the infertility-directed treatment of endometriosis. Well-designed controlled studies are necessary to assess the effectiveness of laparotomy at different stages of disease.

Combination of Conservative Laparotomy and Danazol®

The existing evidence does not support the effectiveness of this intervention in the infertility-directed treatment of endometriosis. Additional well-designed research is needed.

Summary

Ovulation suppression confers no benefit on the infertility-directed treatment of endometriosis when compared with no treatment. The effectiveness of conservative laparotomy with or without the adjuvant use of ovulation suppression is not demonstrated by the limited available data. Although the effect of laparoscopic ablation of endometrial implants is encouraging, it requires further evaluation before its use can be advocated with confidence.

Part 3. Controlled Trials in Assisted Reproductive Technology

Groups of similar studies were identified and subjected to formal meta-analysis in the following areas: gonadotropin-releasing hormone agonists (Gn-RHa) versus traditional ovulation induction protocols (CC/hMG/follicle-stimulating hormone [FSH]) in IVF and GIFT; luteal support with progesterone versus no treatment or placebo; and luteal support with human chorionic gonadotropin (hCG) versus no treatment or placebo.

Gonadropin-Releasing Hormone Agonists

The analyses suggest significant advantages to using Gn-RHa versus traditional ovulation induction protocols. It was found that the routine use of these protocols in IVF and GIFT significantly reduces cycle cancellation, improves the ongoing clinical pregnancy rate, and potentially provides more embryos for transfer in natural cycles following cryopreservation. Further trials of the cost-effectiveness and efficacy of different Gn-RHa protocols may be useful, and the possible increase in multiple pregnancies and ovarian hyperstimulation following this treatment needs to be evaluated. In addition, live-birth outcomes should be considered and reported where possible.

A policy of routine Gn-RHa ovulation induction for IVF and GIFT can be expected to reduce cycle cancellation, improve ongoing clinical pregnancy rates, and provide more embryos for transfer in natural cycles

following cryopreservation. However, clinicians should be aware that the risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancy may be increased with this approach.

Progesterone Luteal Phase Support

The evidence does not support the routine use of luteal phase support with progesterone in patients undergoing IVF or GIFT following CC/hMG/FSH ovulation induction. Further studies of larger sample size may be useful, especially in patients receiving ovulation induction protocols that include Gn-RHa, as these women may be susceptible to corpus luteum dysfunction.

Human Chorionic Gonadotropin Luteal Phase Support

There is evidence of significant benefit from hCG luteal phase support following Gn-RHa ovulation induction protocols. Further studies are warranted to assess efficacy and risk, particularly with respect to OHSS. The data do not support the routine use of hCG in IVF or GIFT following ovulation induction with CC/hMG/FSH; however, as these findings were derived from a small sample size, further trials are also warranted.

Summary

The routine use of Gn-RHa appears to increase the clinical pregnancy rate per treatment cycle by decreasing the rate of cancellation and possibly increasing the rate of embryo implantation. The possibility that these drugs result in increased rates of OHSS and multiple pregnancy deserves further study. Luteal phase support with hCG appears to have a positive effect on ongoing pregnancy rate when used after Gn-RHa treatment. Again, the possibility of increased ovarian hyperstimulation needs to be assessed in further studies. The routine use of progesterone in the luteal phase is not supported by the available evidence. However, even the combined studies have insufficient statistical power to rule out small but clinically significant therapeutic benefit.

Introduction

The results of well-designed clinical studies form the foundation of effective medical care. Regrettably, results of studies addressing the same question are frequently inconclusive or conflicting. Reasons for this include differences between studies in terms of populations, interventions, and outcomes measured, as well as the element of chance. The developing science of meta-analysis provides the tools with which practical answers to clinical questions may be provided through the appropriate combination of the best available evidence. The purpose of this report is to summarize the results of meta-analyses of treatments for unexplained infertility, endometriosis-related infertility, and assisted reproductive technology. A similar format is used in each section, and structured abstracts of all trials included in the overviews appear in Appendices 1-3.

Meta-Analysis: Rationale and Methodology

Numerous interventions have been promoted in the treatment of infertility based largely on "evidence" from uncontrolled case series. Efficacy, however, can be proven only when comparative studies of sound design demonstrate superior pregnancy and birth rates in "treatment" versus "no treatment" groups. Unfortunately, even well-designed, randomized controlled trials in the area of infertility rarely have sufficient statistical power to demonstrate small but clinically significant differences between treatment and control groups. For example, to demonstrate a real difference in clinical pregnancy rate following *in vitro* fertilization (IVF), between 15% in one group and 20% in another, accepting Type I (α) and Type II (β) errors of 0.05 and 0.2 respectively, a study of approximately 1 450 treatment cycles would be necessary. Clearly, trials of this size are difficult to conduct.

An alternative approach to questions not yet answered by large well-designed trials has traditionally been provided by narrative literature reviews. One limitation of these authoritative overviews is the potential for bias in their conclusions, particularly through selection and review of studies that support the authors' beliefs rather than studies that reflect all of the available evidence. A way of addressing this problem is to execute a literature review according to a clearly and prospectively defined protocol, an approach that forms the basis of quantitative overview analysis or meta-analysis. From the clinical reader's standpoint, a major advantage of this type of review is the opportunity to judge the quality of its conclusions. This judgment is based on information about how studies were identified, why they were included, the validity or quality of individual studies, and how their data were extracted and pooled. Meta-analysis has generated considerable interest in the medical literature over the last decade (Sacks et al. 1987; Yusuf et al. 1987; Thacker 1988) and is already a powerful tool in the field of perinatology (Chalmers 1991). With the publication of increasing numbers of well-designed trials, the opportunity now exists to apply this approach to the infertility literature.

Meta-analysis can be divided into four main components: development of a specific question; identification of relevant studies; assessment of study validity; and extraction and appropriate pooling of data. As with all scientific research, a specific and focussed question is of paramount importance. This should include a clear description of the population involved, the intervention used, and the outcome measured. An example of a therapeutic question might be, "In couples with unexplained infertility, does the use of clomiphene citrate (CC) improve the rate of ongoing clinical pregnancy?" The same focussed approach may be used for questions dealing with etiology, diagnosis, and prevention. By refining and defining the question in this way, practical conclusions may ultimately be drawn.

Armed with a specific question, it is first necessary to go over prior reviews because if a recent and well-executed meta-analysis is available, a second may be redundant. Next, relevant published and unpublished literature must be sought. Only when specific search strategies are designed and reported is it possible for the reader to determine whether a meta-analysis is based on the best available evidence. Once identified, studies should be subjected to strict predetermined criteria for inclusion in a meta-analysis based on the components of the research question in terms of population, intervention, outcome, and methodology. In selecting or rejecting articles, a measure of reliability is important to demonstrate a lack of bias. This is best accomplished through an independent assessment of possibly relevant studies by two reviewers using the same predetermined criteria. Differences of opinion may then be resolved by consensus. It is also important to keep a log of rejected articles and publish it as part of the meta-analysis.

The potential for publication bias (bias toward the publication of studies with "positive" results) remains a concern. The omission of negative data, which may arise more frequently from unpublished trials, could lead to an erroneously enhanced "treatment effect." Conversely, inclusion of unpublished data may dilute the quality of a meta-analysis because the data have not passed through a peer review process. An ideal solution would be to completely eliminate the problem of publication bias through the establishment of a registry of planned, randomized control trials. This strategy has been successfully implemented in the field of perinatology (Chalmers 1991). Until the same facility is available to researchers in infertility, a pragmatic approach to the problem of unpublished data is to obtain such data in writing from investigators, funding agencies, and pharmaceutical companies and assess them for relevance and inclusion in the same rigorous fashion as data from published trials.

Once relevant articles have been identified, their methodological strengths and weaknesses or validity can be assessed. The aim of this step is to assess the possibility of bias in study results. Important criteria to consider here include the method, and therefore security, of randomization, the completeness of follow-up, and the possibility of co-intervention. This evaluation should ideally involve two independent reviewers using a pretested scoring system. A measure of agreement between reviewers, as provided by a weighted kappa statistic, gives the reader a sense of how reliably study validity has been measured. The assessment of methodological quality is useful for two main reasons. First, it provides a guide to the strength of any overall conclusions. If none of the included studies was rigorously designed and conducted, then the conclusions of a meta-analysis cannot be drawn with confidence. Conversely, data from methodologically strong studies allow for confident conclusions. Second, if the results of one or more studies are radically different from the others (heterogeneous), an assessment of study validity may provide an explanation for this difference.

The final stage in meta-analysis is the extraction and pooling of data. Primarily to avoid error, data extraction is again best undertaken by two independent reviewers using the same data collection form.

Methods for combining data vary. The basic principle, however, is to generate two-by-two tables for the outcome of interest from each study. These are then used to provide odds ratios or relative risks for the outcome under experimental versus controlled conditions. An odds ratio is an estimate of the likelihood of an event, such as pregnancy, occurring in these two patient groups. Odds ratios may be reported for individual trials or for pooled data. If the lower confidence limit of an odds ratio exceeds the value of one, a positive treatment effect is inferred. Conversely, if the upper confidence limit for this estimate is less than one, a negative treatment effect may be present.

Odds ratios have several statistical advantages as measures of association. They may be combined using an exact statistical test or closely estimated using several established methods, such as the Mantel-Haenszel test (Mantel and Haenszel 1959). Thus, a common odds ratio with 95% confidence limits may be derived, allowing for a quantitative assessment of treatment efficacy. Various methods exist for graphically displaying the common odds ratio and the relative contributions made by each study.

If the results of individual studies are judged to be heterogeneous, either clinically or by statistical testing (e.g., Breslow-Day test [Breslow and Day 1980]), it may not be appropriate to combine them in this way. Under such circumstances, reasons for heterogeneity must be sought. Variability in the quality of the individual studies could be one reason for differing results. It is also possible that some factor or influence that is extraneous to the exposure or treatment under study could be causing both the observed effect and its variability.

Thus, meta-analysis provides a quantitative approach to the review of medical literature. Its critics are quick to point out potential shortcomings, which include concerns over the combination of trials across different populations, interventions, and outcomes — "comparing apples and oranges." Also, the problem of identifying and summarizing all available evidence, thereby avoiding publication bias, remains contentious. Despite such concerns, we believe that through careful application of these techniques, a greater level of agreement may be reached in answering important clinical questions (and identifying areas of ignorance) in reproductive endocrinology and infertility.

Part 1. Controlled Trials in Unexplained Infertility

Introduction

Unexplained infertility is a common condition affecting approximately 26% of Canadian couples presenting to academic infertility centres (Collins and Rowe 1989). Evaluation of the empirical treatments used in this situation is hampered by a number of methodological problems. In the overviews that follow, these problems must be considered.

Definition of Unexplained Infertility

Although a routine infertility investigation includes an assessment of ovulation, tubal patency, and sperm quality, the tests used and the interpretation of their results differ among studies. For this reason, the criteria used for defining unexplained infertility are listed in all treatment overviews. These differences should not, however, lead to the exclusion of trials from overviews, but should draw attention to the potential for bias and the need for a more unified approach to future research.

Treatment-Independent Pregnancy and the Need for Controlled Trials

Treatment-independent pregnancy is a common event. Its reported frequency ranges from 5 to 79% and depends largely on the completeness and duration of follow-up (Collins 1990). In any condition in which a spontaneous cure is possible, a control group is necessary to evaluate treatment efficacy. Through randomization, both known and unknown prognostic factors may be evenly distributed between treatment and control groups, reducing the chance of bias in the results. This report, therefore, focusses on evidence from randomized controlled trials. Studies that compare patient groups assembled concurrently, but not through randomization, provide the next level of evidence. Such cohort studies are prone to selection bias because admission to one treatment group or another is often based on patient or physician preference, or a particular factor that may itself be of prognostic importance. Prospective cohort studies have the advantage of clearly defined inclusion and exclusion criteria, which are applied to all patients prior to study entry. In this way, groups may be clearly defined, although they are still likely to differ in terms of prognostic factors.

Cohort studies assembled in a retrospective way compare outcomes in patient groups identified after treatment has been completed. Although this design may provide useful information on the course of disease, it is rarely helpful in answering questions dealing with treatment efficacy. Cohort studies have been included only in the absence of more rigorous data.

The final class of research is regrettably the largest: uncontrolled case series. Although such studies may be useful in defining the incidence of adverse treatment outcomes, they are of no use in determining treatment efficacy and are excluded from all overviews.

Potential Threats to Study Validity

Randomization Method

Although many studies report random treatment allocation, they often fail to note or appreciate the importance of the method used. Bias may be introduced through insecure treatment allocation, for example, an open random table, patient identification number, or date of treatment. The method of randomization has been considered as the primary validity criterion for all studies included in overviews.

Sample Specification

Clearly defined inclusion and exclusion criteria are necessary in any study. Without information on factors such as age and duration of infertility, the clinical reader is unable to assess whether the intervention as described has potential for the same level of efficacy when applied to a different patient population.

Manoeuvre

The intervention should also be clearly specified. Sufficient information should be given to allow its exact reproduction. When dealing with a drug trial, a double-blind approach is preferable. With other forms of intervention, this may not be possible.

Outcome

The primary outcome of interest should be specified at the outset of the trial. Although pregnancy is a clear and dichotomous variable, it should be exactly defined in terms of beta human chorionic gonadotropin (ßhCG) level, ultrasound findings, tissue on curettage, or live birth. Once again, only through a clear description of the outcome can results be extrapolated to other populations.

Completeness of Follow-Up

When pregnancy occurs, the successful couple is excluded from further follow-up. Similarly, incomplete follow-up as a result of patient migration or disinterest reduces the size of the final denominator. In trials of greater than three months' duration, survival analysis provides more information than a comparison of crude pregnancy rates. Through these techniques, incomplete follow-up due to drop-out or pregnancy is taken into account. This approach is particularly useful in trials of unexplained and endometriosis-related infertility. In trials of short duration, commonly seen in association with assisted reproductive technology, comparison of pregnancy rates per cycle is more acceptable. However, exclusion of even

a small proportion of the data (> 5% of subjects enrolled) may result in significant bias.

Crossover Studies

Results from crossover studies are also subject to bias through drop-out and incomplete follow-up. Patients becoming pregnant during the first phase of a crossover trial following treatment A are not available during the second phase to receive treatment B or placebo. Because the relatively more fecund group may be eliminated before crossover, a form of selection bias is introduced. In comparing treatment and control groups, therefore, it is more appropriate to consider only the first phase of crossover trials in an overview. This has been the approach adopted wherever possible in this report. Where data cannot be separated, this has been pointed out in the text.

Duration of Follow-Up

Data from the Canadian Infertility Treatment Evaluation Study (Collins 1989) clearly demonstrate that fecundity during the early months of follow-up is higher than during later months. When 381 untreated couples with unexplained infertility were followed for six months, their mean fecundity per cycle was 4%. In the subsequent six months, this level fell to 2%. Those patients followed for a maximum of six months had a mean monthly fecundity of 22%. This relatively high fecundity rate observed during the early period of untreated follow-up compares favourably with fecundity rates observed in uncontrolled studies of active treatments, such as intrauterine insemination (IUI) and ovarian hyperstimulation. Such case series involve short periods of treatment, usually of one to six cycles, a factor that again underlines the need for controlled trials.

Protocol for Meta-Analyses in Unexplained Infertility

Research Questions

In infertile couples experiencing unexplained infertility, do commonly used treatments improve the rate of conception?

Population: Couples experiencing infertility for a period of ≥ 1 year and for whom ovulation, pelvic architecture, and sperm quality have been assessed by clearly defined tests and found to have no demonstrable abnormality.

Interventions: Danazol®, bromocriptine, superovulation with clomiphene, IUI, superovulation with human menopausal gonadotropin (hMG) ± IUI, and IVF and gamete intrafallopian transfer (GIFT).

Primary Outcome: Clinical pregnancy defined by a positive pregnancy test, ultrasound imaging of a gestational sac, and/or products of conception on curettage.

Study Identification

1. Retrospective journal hand-search: Forty-one core journals have been hand-searched in collaboration with the Leeds University group from January 1980 to January 1990 using the following selection criteria: (a) randomized or quasi-randomized controlled trials; (b) therapeutic intervention in infertile couples; and (c) pregnancy, a defined and reported outcome.
2. Prospective hand-search beginning in January 1990: Forty-one core journals were prospectively hand-searched using the same selection criteria as described above.
3. MEDLINE search: Studies were identified through the National Library of Medicine MEDLINE data base using medical subject headings "unexplained infertility" and "pregnancy."
4. Bibliographies from retrieved articles were hand-searched for relevant articles.
5. Abstracts from relevant North American and European scientific meetings (1986-1991) were hand-searched for recent and as yet unpublished trials.

Strategy for Study Retrieval

Two independent reviewers (EGH and JAC) reviewed the hand-searches and MEDLINE search. Any study potentially fulfilling the inclusion criteria was copied and retrieved.

Inclusion Criteria

1. Population and interventions as described.
2. Methodology: Only randomized controlled trials and cohort studies were included.

Strategy for Study Inclusion

Articles were copied in full without blinding of the author to the journal. Methods sections of potentially relevant articles were reviewed independently by EGH and JAC, and inter-observer agreement was measured by kappa (0.83) for a pilot study of 24 manuscripts.

Validity Criteria Score

The following four criteria were considered to be the most important in terms of posing a threat to study validity. The scores afforded each study appear below the first author's name in each table and figure.

1. Randomization procedure
   (a) randomized by central means (telephone or pharmacy)
   (b) randomized by sealed accounted envelope
   (c) randomization method other than above, method not described, or day of month, date of birth, or clinic chart number (quasi-randomization) used

2. Follow-up
   (a) outcome data used for primary analysis complete — all randomized patients accounted for, with "intention to treat" analysis
   (b) outcome data incomplete, with < 5% of cycles commenced having outcome data missing
   (c) outcome data incomplete, with > 5% of cycles commenced having outcome data missing

3. Crossover trial?
   (a) no crossover, or data from first treatment period available
   (b) crossover occurred and data from treatment periods combined

4. Co-intervention?
   (a) other than for use of treatment and control, protocols were similar
   (b) difference in protocol in addition to treatment versus control

Data Extraction

This was undertaken independently by both authors (EGH, JAC), and results were checked for errors.

Data Analysis

Common odds ratios were generated for the variables of interest using the Mantel-Haenszel method (Mantel and Haenszel 1959). This provides a robust approximation of the common odds ratio with conservative estimates of confidence limits.

Heterogeneity has been assessed in all overviews. From a clinical standpoint, differences in population intervention and outcome have been highlighted. The level of statistical heterogeneity based on results of the Breslow-Day test (Breslow and Day 1980) has also been reported.

Overview Number: 1 (Table 1, Figure 1)

Title: **Bromocriptine Versus Placebo in the Treatment of Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Editorial Commentary

1. **Objective**: To determine the efficacy of bromocriptine in the treatment of unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Randomized controlled trials comparing bromocriptine with placebo or no treatment in couples with unexplained infertility as previously defined.
3. **Trials excluded**: Lenton et al. (1977) — no control group.
4. **Trials included**: Wright et al. (1979); McBain and Pepperell (1982).
5. **Unpublished data**: None identified.
6. **Methodological quality**: Both of these trials were double-blind and centrally randomized by pharmacy. Both had small sample sizes (< 50 patients). Follow-up in the trial of Wright et al. (1979) was reported as complete, but it was not possible to determine whether the same was true for the study of McBain and Pepperell (1982). The latter trial also used a crossover design after three treatment cycles, and data from the treatment periods were not separable.
7. **Results**: Neither of these studies demonstrated improved conception rates following bromocriptine treatment — common odds ratio 1.25 (95% confidence interval [CI] 0.46-3.37), suggesting that in this patient population, bromocriptine is not useful. It may, however, be of some value in normoprolactinemic women with expressible galactorrhoea and unexplained infertility (DeVane and Guzick 1986). A cohort study reported a higher conception rate in such women when treated with bromocriptine compared with pyridoxine (n = 43). However, women in the control group were older, had a longer period of infertility, and had lower basal prolactin levels, making the validity of this conclusion questionable.
8. **Consistency of results across trials**: Clinically and statistically, these data appear to be homogeneous.
9. **Risks and costs**: The common side-effects of bromocriptine are nausea and hypotension. Based on data from 1 410 pregnancies, there appears to be no increased risk of fetal anomaly or spontaneous

abortion (Briggs et al. 1990). The estimated direct cost per treatment cycle (2.5 mg daily for 30 d) is $26.10.*

10. **Implications for practice**: There is no apparent benefit from bromocriptine use in women with unexplained infertility.

11. **Implications for research**: Larger trials examining this question in specific subgroups, for example, normoprolactinemic women with unexplained infertility and galactorrhoea, may be warranted. Clearly, this would require a multicentre approach.

12. **Conclusions**: Bromocriptine is not an effective treatment in unselected normoprolactinemic women with unexplained infertility.

* All drug costs quoted in this report are based on wholesale prices, exclusive of pharmacy overhead and prescribing charges.

Table 1. Randomized Controlled Trials Comparing Bromocriptine with Placebo in Women with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Wright 1979 3/3/2/2	Central randomization by pharmacy Double-blind	24 (24)	23 (23)	Type infertility[a] Ovulation[cd] Tubal status[e] or [f] Sperm[g] Post-coital test[y]	Bromocriptine 2.5 mg twice daily (BID) 6 months	Placebo tablet BID 6 months	Serum estradiol; progesterone; prolactin; pregnancy	6 months post-treatment	Cumulative pregnancy rates reported
McBain 1982 3/1/1/2	Central randomization by pharmacy Double-blind	25 (?)	25 (?)	Type infertility[b] Ovulation[z] Tubal status[f] Sperm[z] Post-coital test[y]	Bromocriptine 2.5 mg BID 3 months	Placebo tablet BID 3 months	Serum progesterone; estradiol; pregnancy	12 months post-treatment	Crossover trial Compliance checked by counting tablets

[a] primary
[b] primary or secondary
[c] basal body temperature chart
[d] luteal serum progesterone
[e] hysterosalpingogram
[f] laparoscopy
[g] count > 20 x 10^6/mL
[y] "normal"
[z] not stated

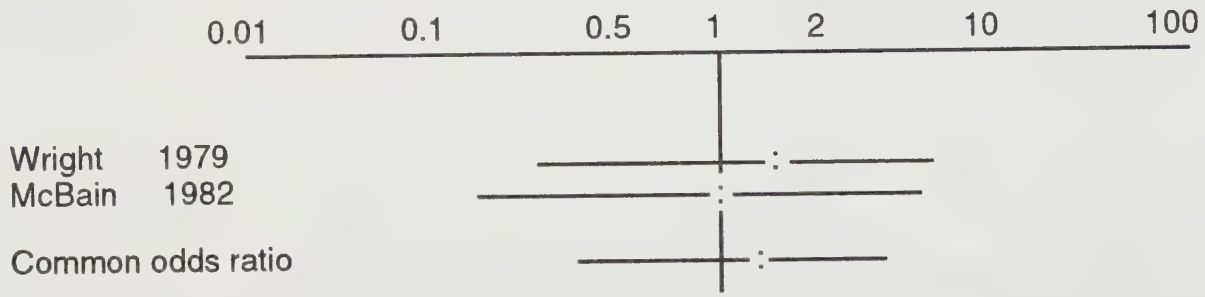
Figure 1. Randomized Controlled Trials Comparing Bromocriptine with Placebo in Women with Unexplained Infertility

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Wright	1979	7	24	5	23	1.48	0.33	6.81	0.56
3/1/1/2	McBain	1982	4	25	4	25	1.00	0.17	5.67	1.00
Common odds ratio and 95% CI							1.25	0.46	3.37	0.66

Breslow-Day = 0.147, p = 0.701

* p value based on Mantel-Haenszel corrected chi-square



Overview Number: 2 (Table 2, Figure 2)

Title: **Danazol® Versus Placebo in the Treatment of Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Editorial Commentary

1. **Objective**: To determine the efficacy of Danazol® in the treatment of unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Randomized controlled trials comparing Danazol® with placebo or no treatment in couples with unexplained infertility as previously defined.
3. **Trials excluded**: Greenblatt et al. (1974) — no control comparison.
4. **Trials included**: vanDijk et al. (1979); Iffland et al. (1989).
5. **Unpublished data**: None identified.
6. **Methodological quality**: Although neither of these studies stated the method of randomization used, both appear to be randomized double-blind trials. vanDijk et al. (1979) reported complete follow-up among 40 couples, but excluded one patient from the analysis (placebo group) because she conceived during the six-month treatment phase rather than during the six-month post-treatment period. This questionable decision undermines the validity of their conclusions. Iffland et al. (1989) described the eight patients who left their trial post-randomization, but did not report the pregnancy rate in this group. Interestingly, although side-effects were reported with a similar frequency between groups in this study, more women dropped out of the Danazol® group than the placebo group, leaving 11 and 17 women, respectively. Neither trial used a crossover design, and co-intervention did not appear to be present.
7. **Results**: These trials reach different conclusions. Based on the exclusion of one pregnancy from the placebo group, vanDijk et al. (1979) reported a significant improvement in pregnancy with Danazol® (Fisher's exact $\chi^2 = 4.91$, $p < 0.05$). However, the more appropriate approach would be to include this patient, rendering the treatment effect non-significant ($\chi^2 = 1.4$, $p = 0.237$). Iffland et al. (1989) reported no pregnancy in the 12 months following Danazol® and one pregnancy following placebo. The common odds ratio for these trials was 2.84 (95% CI 0.509-12.8), suggesting no significant treatment benefit.
8. **Consistency of results across trials**: The Breslow-Day test demonstrates no statistically significant heterogeneity between these

data. Any that exists is likely to be a function of chance and differing patient populations.

9. **Risks and costs**: Common side-effects of Danazol® include weight gain and oily skin. Rarely, hirsutism and clitoromegaly occur. This drug is contraindicated in pregnancy because of the risk of virilization of the fetus (Kingsbury 1985; Quagliarello and Greco 1985). The estimated direct cost for three months of treatment (200 mg/d) is $145.80.

10. **Implications for practice**: Danazol® given in a low dose does not appear to improve the outcome in unexplained infertility. Its efficacy is unproven and its effects potentially detrimental. During treatment, contraception must be used, thus eliminating the chance of spontaneous pregnancy. Side-effects and cost are also concerns.

11. **Implications for research**: Larger trials do not appear to be warranted based on these findings.

12. **Conclusions**: Danazol® (200 mg daily) is not indicated in the treatment of unexplained infertility.

Table 2. Randomized Controlled Trials Comparing Danazol® with Placebo in Women with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
vanDijk 1979 1/2/2/2	Randomized, method not stated Double-blind	21 (21)	19 (19)	Type infertility[z] Ovulation[c or d] Tubal status[e and f] Semen[y] Post-coital test[y]	Danazol® 200 mg daily for 6 months	Placebo tablet daily for 6 months	Serum gonadotropin; prolactin; estradiol; progesterone; pregnancy	6 months post-treatment	Authors' analysis excluded one pregnancy in placebo group
Iffland 1989 1/1/2/2	Randomized, method not stated	? (11)	? (17)	Type infertility[a] Ovulation[d] Tubal status[f] Semen[gh] Post-coital test[z]	Danazol® 200 mg daily for 12 weeks	Placebo tablet daily for 12 weeks	Haematologic and liver function tests; pregnancy	12 months post-treatment	Eight patients excluded from analysis because of patient withdrawal or biochemical abnormality

[a] primary
[c] basal body temperature chart
[d] luteal serum progesterone
[e] HSG
[f] laparoscopy
[g] count > 20 x 10^6/mL
[h] motility > 40%
[y] "normal"
[z] not stated

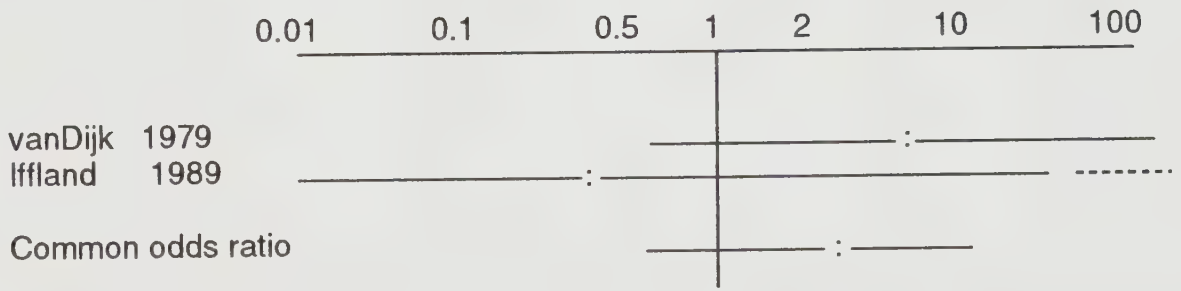
Figure 2. Randomized Controlled Trials Comparing Danazol® with Placebo in Women with Unexplained Infertility

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/2/2/2	vanDijk	1979	5	21	1	19	5.62	0.52	141	0.24
1/1/2/2	Iffland	1989	0	11	1	17	0.48	0.00	22 000	0.82
Common odds ratio and 95% CI							2.84	0.51	12.8	0.44

Breslow-Day = 2.20, p = 0.138

* p value based on M-H corrected chi-square



Overview number: 3 (Table 3, Figures 3.1-3.3)

Title: **Clomiphene citrate (cc) Versus Placebo in the Treatment of Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Editorial Commentary

1. **Objective**: To determine whether clomiphene citrate improves the rate of conception in couples with unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Randomized controlled trials comparing clomiphene with placebo or no treatment in women with unexplained infertility as previously defined.
3. **Trials excluded**: Corsan and Kemmann (1991); Bongers et al. (1991); Koninckx et al. (1984); Martinez et al. (1990); Randall and Templeton (1991); Yavetz et al. (1990) — no concurrent control group or usable data.
4. **Trials included**: Fisch et al. (1989); Deaton et al. (1990); Glazener et al. (1990); Harrison and O'Moore (1983).
5. **Unpublished data**: None identified.
6. **Methodological quality**: The quality of randomization among the studies is variable. Only the trial reported by Fisch et al. (1989) used central randomization in a double-blind fashion. This trial also gave the most complete "intention to treat" analysis of data from all randomized subjects. The other three trials used crossover designs. It was possible to extract data from the first treatment period only from the studies of Deaton et al. (1990) and Harrison and O'Moore (1983).

   There were important differences in patient populations among the studies. Patients with surgically treated endometriosis were included in the trial by Deaton et al. (1990), giving rise to concern over co-intervention (see endometriosis overviews in Part II of this report). The median duration of infertility in the study of Glazener et al. (1990) was relatively short — only 28 months — whereas Fisch et al. (1989) included only patients with primary infertility. Although the latter trial used clomiphene in association with hCG, it was possible to evaluate the data from the clomiphene-only treatment arm. Only these data have been included in the current overview. The same cannot be said for the trial of Deaton et al. (1990). In this study, all patients receiving clomiphene also underwent IUI. Although IUI does not appear to have any clear benefit in unexplained infertility, its inclusion may lead to biased results.

7. **Results**: The study of Fisch et al. (1989) reported a statistically significant improvement in the pregnancy rate following clomiphene versus placebo ($p < 0.05$). This difference was, however, based on the absence of pregnancy in the placebo group of 36 patients during the four cycles of observation. In the six months that followed, seven pregnancies occurred in this group. Clearly, the element of chance has had a major effect on the outcome of this trial.

   The results of the less rigorously designed studies were also encouraging. Deaton et al. (1990) reported a significant improvement in the cumulative conception rate following clomiphene and IUI. Glazener et al. (1990) observed a significant benefit from clomiphene only in couples experiencing infertility for more than three years. This subgroup analysis was described prospectively in the methods section as a secondary objective.

   When data from the four trials reporting pregnancy per patient were combined, the common odds ratio was 2.61 (95% CI 1.49-4.54), suggesting a significant treatment effect. Similar figures were obtained by combining data from the four studies reporting conceptions per cycle — common odds ratio 2.52 (95% CI 1.49-4.26). When only cycles prior to crossover were included from three studies (Harrison and O'Moore 1983; Fisch et al. 1989; Deaton et al. 1990), the common odds ratio was also significantly greater than unity at 6.56 (95% CI 2.14-20.1).

8. **Consistency of results across trials**: Although the Breslow-Day test for homogeneity showed no statistically significant differences among the data, differences in populations clearly exist.

9. **Risks and costs**: The risk of multiple pregnancy is increased with clomiphene use to approximately 10% (Serono Canada Limited 1990). Ovarian cyst formation may occur, and monitoring of symptoms and ovarian size is recommended. Although no increases in spontaneous abortion or fetal abnormality have been demonstrated, women should be counselled to avoid clomiphene following an abnormal or missed period, thereby reducing the risk of fetal exposure during pregnancy (Alexander and Cotanch 1980; Lobo et al. 1982; Serono Canada Limited 1990). The estimated direct cost per treatment cycle (50 mg for 5 d) is $21.80.

10. **Implications for practice**: These data support the use of clomiphene in patients with unexplained infertility. However, the strength of this conclusion is not great, based on the inconsistent quality of the trials.

11. **Implications for research**: Large, randomized controlled trials of parallel design are warranted to further assess this intervention. These should also address the questions of optimal dose and responses in different patient subgroups.

12. **Conclusions**: Clomiphene citrate use in women significantly improves the rate of conception in couples with unexplained infertility. Because of the ease of administration, relatively low cost, and low incidence of side-effects, clomiphene should be used as a primary treatment in this patient group. It may be more effective, however, in women with a period of infertility exceeding three years.

Table 3. Randomized Controlled Trials Comparing Clomiphene with Placebo in Women with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Fisch 1989 3/3/2/2	Randomization, double-blind trial Treatment allocated by coordinating centre	? (37)	? (36)	Type infertility[a] Ovulation[cd] Tubal status[f] Sperm[gh] Post-coital test[z]	Clomiphene 100 mg days 5-9	Placebo two tablets days 5-9	Pregnancy	6 months post-treatment	Part of a four-arm trial including hCG luteal support Multicentre trial in five Canadian university centres
Glazener 1990 3/1/1/2	Randomized double-blind, but method of allocation not described	? (109)	? (105)	Type infertility[b] Ovulation[z] Tubal status[f] in some patients Sperm[z] Post-coital test[y]	Clomiphene 100 mg days 2-6	Matching placebo two tablets days 2-6	Serum progesterone Pregnancy	Six treatment cycles only	Crossover design Not all patients underwent tubal assessment Semen quality was not described

Table 3. (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Harrison 1983 1/3/2/1	Randomized, method not described	15 (15)	15 (15)	Type infertility[b] Ovulation[d] Tubal status[e and f] Sperm[y] Post-coital test[y]	Clomiphene 100 mg x 4 d + hCG 5 000 International Units (IU) day 12	Placebo two tablets x 4 d + hCG 5 000 IU day 12	Side-effects; pregnancy; spontaneous abortion	Up to 12 treatment cycles	Crossover design All patients received three cycles of clomiphene alone before randomization
Deaton 1990 1/1/1/1	Randomized, method not described	? (46)	? (40)	Type infertility[b] + treated endometriosis Ovulation[c] Endometrial biopsy[y] Sperm[ghi] Post-coital test[y]	Clomiphene 50 mg days 5-9 + timed IUI	Intercourse around time of ovulation	Pregnancy	Eight treatment cycles only	Co-intervention with IUI Crossover design Some women had endometriosis treated surgically before randomization

b primary or secondary
c basal body temperature chart
d luteal serum progesterone
f laparoscopy
g count > 20 x 10^6/mL
h motility > 40%
x "abnormal"
y "normal"
z not stated

Figure 3.1 Randomized Controlled Trials Comparing Clomiphene with Placebo or No Treatment in Women with Unexplained Infertility in Terms of Pregnancy per Patient Analyzed

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Fisch[1]	1989	7	37	0	36	17.9	1.38	999	0.02
3/1/1/2	Glazener[2]	1990	24	109	15	105	1.69	0.79	3.66	0.20
1/3/2/1	Harrison[2]	1983	5	30	1	27	5.2	0.55	101	0.25
1/1/1/1	Deaton[2]	1990	14	46	5	40	3.06	0.89	11.1	0.08
Common odds ratio and 95% CI							2.61	1.49	4.54	0.0009

Breslow-Day = 0.147, p = 0.701

*p value based on M-H corrected chi-square

[1] Clomiphene versus placebo, excluding cycles with hCG

[2] Includes first and second treatment periods in crossover trials

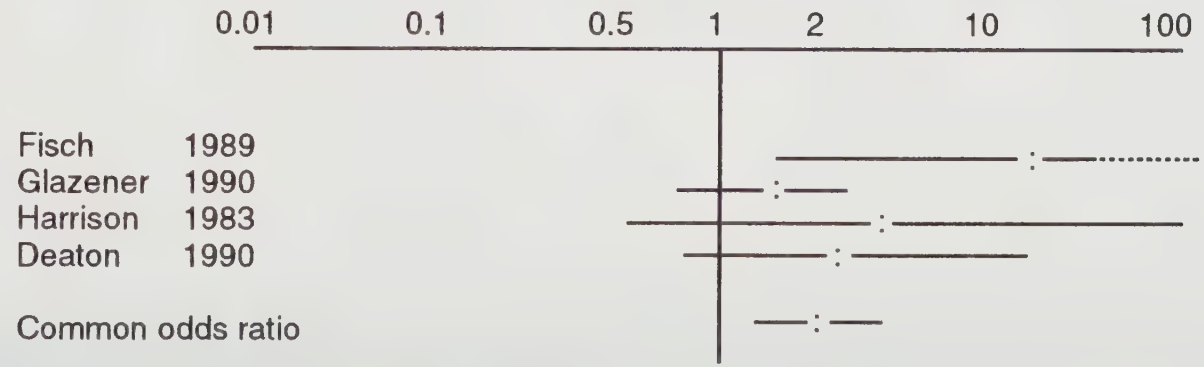


Figure 3.2 Controlled Trials Comparing Clomiphene with Placebo or No Treatment in Couples with Unexplained Infertility in Terms of Pregnancy per Treatment Cycle (Post-Crossover Cycles Included)

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Fisch[1]	1989	7	136	0	144	16.7	1.39	999	0.018
3/1/1/2	Glazener[2]	1990	24	295	15	295	1.65	0.86	3.39	0.18
1/3/2/1	Harrison[2]	1983	5	159	1	158	5.09	0.57	1 116.7	0.22
1/1/1/1	Deaton[2]	1990	14	148	5	150	3.03	0.98	900	0.54
Common odds ratio and 95% CI							2.52	1.49	4.26	0.66

Breslow-Day = 5.17, p = 0.16

* p value based on M-H corrected chi-square

[1] Clomiphene versus placebo, excluding cycles with hCG

[2] Includes first and second treatment periods in crossover trials

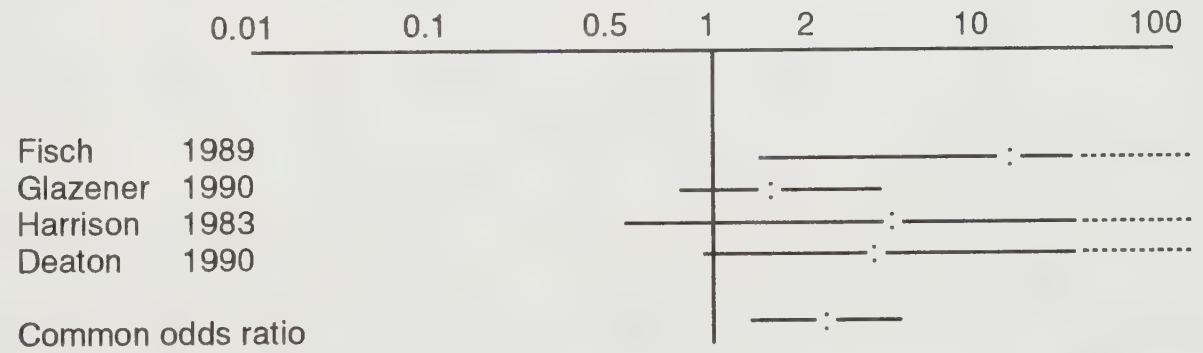


Figure 3.3 Controlled Trials Comparing Clomiphene Versus Placebo or No Treatment in Couples with Unexplained Infertility in Terms of Pregnancy per Treatment Cycle (Post-Crossover Cycles Excluded)

Method: Odds Ratio (Mantel-Haenszel)

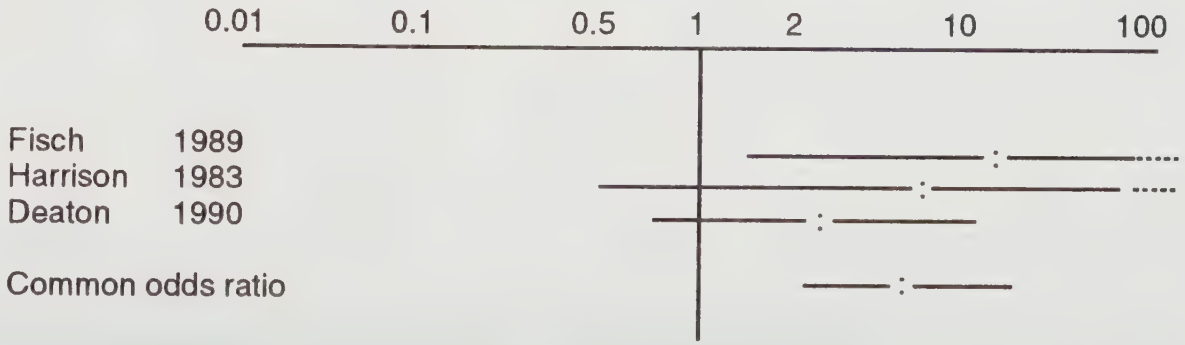
			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Fisch[1]	1989	7	136	0	144	16.7	1.39	999	0.02
1/3/2/1	Harrison[2]	1983	3	79	0	90	8.28	0.51	999	0.20
1/1/1/1	Deaton[2]	1990	8	73	4	103	3.05	0.79	12.6	0.13
Common odds ratio and 95% CI							6.56	2.14	20.06	0.0007

Breslow-Day = 3.264, p = 0.515

* p value based on M-H corrected chi-square

[1] Clomiphene versus placebo, excluding cycles with hCG

[2] Includes first treatment cycles in crossover trials



Overview Number: 4 (Table 4, Figure 4)

Title: **IUI Versus Timed Intercourse in Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Editorial Commentary

1. **Objective**: To determine whether IUI improves the pregnancy rate when compared with timed intercourse in couples with unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Randomized controlled trials addressing the above question.
3. **Trials excluded**: Hughes et al. (1987); Ho et al. (1989); Kerin et al. (1984); te Velde et al. (1989) — randomized treatment allocation, but data on patients with unexplained infertility not included.
4. **Trials included**: Martinez et al. (1990); Kirby et al. (1991).
5. **Unpublished data**: None identified.
6. **Methodological quality**: The study of Martinez et al. (1990) has significant methodological limitations. Four treatment approaches were planned for each patient, to be given over a four-cycle period. Patients were randomized to commence treatments in different sequences (n = 8), although the method of randomization was not reported. The effect of dropping out because of pregnancy in such a crossover trial introduces the potential for significant bias, as described in the introduction to this report. The study of Kirby et al. (1991) also employs a crossover design, but reports data per cycle. One concern with this trial is that intercourse was not recommended until 40 h after the onset of a spontaneous luteinizing hormone (LH) surge, determined by serum testing. This may have reduced the potential for spontaneous conception.
7. **Results**: Neither study demonstrated significant benefit from IUI in this patient group. The common odds ratio for pregnancy following treatment was 2.10 (95% CI 0.635-8.36).
8. **Consistency of results across trials**: The patient population in the study of Kirby et al. (1991) differed in terms of sperm quality from other studies of unexplained infertility (concentration > 40×10^6/mL). However, there was no statistically significant heterogeneity demonstrated (Breslow-Day = 0.244, p = 0.622).
9. **Risks and costs**: The most important potential side-effect of IUI is pelvic infection — no cases have been reported, however, in the trials cited. IUI does not appear to cause anti-sperm antibody formation. The direct cost per treatment cycle at Chedoke-McMaster Hospital is $55.00-$110.00.

10. **Implications for practice**: Because of the limited power and quality of these data, conclusions should be drawn with caution. The data suggest that in couples with unexplained infertility, IUI is not helpful. However, cohort studies suggest significant benefit in women with infertility caused by a cervical mucus factor (Margalloth et al. 1988; te Velde et al. 1989). Because mucus-sperm interaction tests are of little value in predicting pregnancy (Collins 1988), it may be worthwhile using IUI for a limited number of cycles, perhaps up to six, in couples with otherwise unexplained infertility.
11. **Implications for research**: Additional well-designed studies are warranted to address the efficacy of IUI in unexplained as well as other types of infertility.
12. **Conclusions**: IUI has no proven benefit among couples with unexplained infertility.

Table 4. Randomized Controlled Trials Comparing IUI with Timed Intercourse in Couples with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Kirby 1991 1/1/2/1	Randomized, method not described	? (145)	? (123)	Type infertility[b] Ovulation[z] Tubal status[f] Sperm count > 40 x 10^6/mL Motility > 45% Morphology > 40%	Swim-up or percoll wash + IUI	Intercourse	Pregnancy	Up to six treatment and control cycles	Crossover trial Insemination + intercourse timed by daily LH assay Intercourse recommended 40 h after LH surge
Martinez 1990 1/1/1/1	Randomized, method not described	21 (?)	21 (?)	Type infertility[b] Ovulation[c] Tubal status[ef] Sperm[y] Post-coital test[y]	Prewashed sperm + IUI, with or without clomiphene	Time intercourse, with or without clomiphene	Pregnancy	Four treatment cycles only	Crossover trial using four treatment approaches, not possible to separate data for each

[b] primary or secondary
[c] basal body temperature chart
[e] HSG
[f] laparoscopy
[y] "normal"
[z] not stated

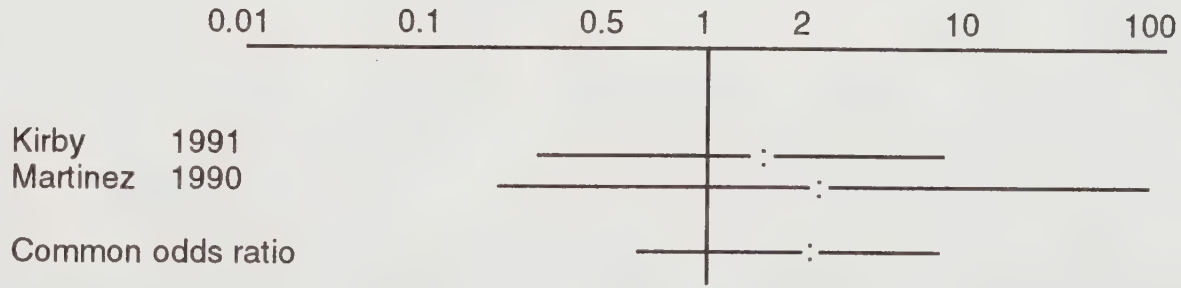
Figure 4. Randomized Controlled Trials Comparing IUI with Timed Intercourse in Couples with Unexplained Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Observations	Total	Observations	Total		Lo	Hi	
1/1/2/1	Kirby	1991	6	145	3	123	1.72	0.374	8.92	0.67
1/1/1/1	Martinez	1990	3	33	1	35	3.40	0.288	98.7	0.53
Common odds ratio and 95% CI							2.10	0.635	8.36	0.34

Breslow-Day = 0.244, p = 0.622

* p value based on M-H corrected chi-square



Overview Number: 5 (Table 5.1 and 5.2, Figures 5.1 and 5.2)

Title: **hMG With or Without IUI Versus Placebo in Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Parts of this overview:

1. hMG ± IUI versus hMG plus timed intercourse (three trials)
2. hMG ± IUI versus IUI alone or timed intercourse (three trials)

Editorial Commentary

1. **Objective**: To determine whether hMG alone or in combination with IUI is an effective treatment in unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Because of the limited data available, randomized controlled trials and cohort studies comparing hMG plus IUI with hMG, IUI alone, or timed intercourse were included.
3. **Trials excluded**: Chaffkin et al. (1991) — relevant data on unexplained infertility patients reported in the methods section of the text and in Table 1 are inconsistent; Martinez et al. (1991) — treatment comparisons not relevant to the research question posed; Dodson and Haney (1991) — no control comparison.
4. **Trials included**: Randomized controlled trials: Crosignani et al. (1991); Evans et al. (1991); Nulsen et al. (1990). Cohort studies: Serhal et al. (1988); Welner et al. (1988); Daly (1989).
5. **Unpublished data**: None identified.
6. **Methodological quality**: Two randomized controlled trials compared hyperstimulation plus IUI with hyperstimulation plus intercourse (Crosignani et al. 1991; Evans et al. 1991). The first study involved 19 centres and compared five different treatment approaches. Each centre was asked to select two treatments and conduct a randomized study of these (Crosignani et al. 1991). Data were then pooled from all centres. The methodological concerns associated with this study include heterogeneity of populations and interventions. In addition, there was crossover. If not pregnant during the first treatment cycle, patients received the alternate treatment (only data from the first treatment cycle are included in this overview). Lastly, the method of randomization was not reported. The second study compared three treatment arms and again used a crossover design (Evans et al. 1991). "Crossover" also occurred within groups post-randomization, when technical problems precluded an individual treatment. For example, when IUI was not possible, direct intraperitoneal insemination (DIPI) was done instead. A third study compared hMG plus IUI with IUI

alone (Nulsen et al. 1990). It is published in abstract form only, so a full methodological assessment is not possible. However, a crossover design was used, and it is not possible to extract data from the first treatment cycle.

The remaining studies used prospective or retrospective cohort designs (Serhal et al. 1988; Welner et al. 1988; Daly 1989). There were significant inconsistencies among age, duration of infertility, and follow-up in these cohort groups.

7. **Results**: *Part 1.* Crosignani et al. (1991) reported a cycle fecundity of 27.1% with hMG plus IUI versus 17.4% with hMG plus intercourse. Fecundity rates following one cycle of IVF, GIFT, or hMG plus DIPI were between 23.7 and 29.9%. When data from 338 cycles of hMG plus IUI, IVF, GIFT, or DIPI were compared with 106 cycles of hMG plus intercourse, the difference in fecundity bordered on statistical significance ($p = 0.058$). All five treatment approaches, however, resulted in pregnancy rates superior to the estimated 2% per cycle rate expected with no treatment in this patient group. Evans et al. (1991) also compared ovarian hyperstimulation (CC/hMG) plus IUI with hyperstimulation plus intercourse. They demonstrated no significant difference in outcomes with or without IUI (2/27 versus 1/26). The third study dealing with this issue used a retrospective cohort design (Serhal et al. 1988). This study suggested a significant improvement with hMG/IUI versus hMG plus intercourse. The common odds ratio for data addressing this issue was 2.35 (95% CI 1.11-4.98) with the cohort study excluded and 2.65 (95% CI 1.34-5.26) with it included.

   Part 2. Four trials compared hMG plus IUI with either IUI alone or intercourse. Only one used a randomized controlled design (Nulsen et al. 1990). A significant improvement was demonstrated with the combination hMG plus IUI versus IUI alone ($p = 0.012$). When these data are combined with those from the three cohort studies (Serhal et al. 1988; Welner et al. 1988; Daly 1989), the common odds ratio was 2.45 (95% CI 1.17-5.14).

8. **Consistency of results across trials**: The data from hMG plus IUI versus hMG plus intercourse trials were statistically homogeneous (Breslow-Day = 0.79, $p = 0.94$). Crosignani et al. (1991) and Evans et al. (1991) used similar designs and had similar populations in terms of age and duration of infertility. In the overview of hMG plus IUI versus IUI alone, the data are statistically heterogeneous (Breslow-Day = 8.78, $p = 0.03$). This probably reflects the cohort design of three of the trials and again underlines the concern that any conclusions from these should be drawn with caution.

9. **Risks and costs**: The risk of multiple pregnancy following gonadotropin therapy is approximately 20% (Diamond and Wentz 1986). Moderate to severe ovarian hyperstimulation occurs in 1-3% of patients, who may, as a result, require hospital admission. Long-term follow-up studies are required to assess the effect of hMG on ovarian function. The direct cost per treatment cycle (hMG 10 ampoules plus IUI) is approximately $700.00. Additional costs associated with the estradiol assay and ovarian ultrasound should also be considered.

10. **Implications for practice**: The combination of hMG plus IUI versus hMG plus intercourse, IUI alone, or intercourse alone may be beneficial.

11. **Implications for research**: This is an important area for further study. Small treatment benefits may exist, but at the potential cost of significant side-effects, for example, ovarian hyperstimulation and multiple pregnancy. Very few data were available on either of these outcomes.

12. **Conclusions**: In couples with unexplained infertility, there appears to be some benefit from hMG plus IUI versus hMG plus intercourse. In studies comparing hMG plus IUI versus intercourse or IUI, data are heterogeneous and of poor quality. The common odds ratio suggesting an overall treatment benefit should therefore be read with caution.

Table 5.1 Controlled Studies Comparing hMG plus IUI with hMG Alone in Couples with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Crosignani 1991 1/3/2/2	Random allocation, method not described	158 (158) patients	78 (78)	Type infertility[b] Ovulation[d] Tubal status[e] Sperm[ghi] < 38 years of age (female) > 3 years infertility Abstain from intercourse around treatment	hMG + IUI	hMG alone	Pregnancy	Two treatment cycles	Crossover study, but data from first cycle reported separately
Evans 1991 1/1/1/2	Random allocation, method not described	? (16) cycles	? (26)	Type infertility[b] Ovulation[z] Tubal status[z] Sperm[gh] Anti-sperm antibody[y] Post-coital test[y]	CC/hMG + IUI	CC/hMG + timed intercourse	Pregnancy	Up to four cycles within each treatment group	Crossover trial of three treatments (including DIPI) Data from first part of study included — second part

Serhal 1988 0/3/2/2	Retrospective cohort	19 (19) cycles	30 (30)	Type infertility[b] Ovulation[cd] Tubal status[f] Sperm[ghi] Post-coital test[y]	hMG ± IUI	IUI alone	Pregnancy	Study period only One to two cycles per couple	Results reported per patient and per cycle

[b] primary or secondary
[c] basal body temperature chart
[d] luteal serum progesterone
[e] HSG
[f] laparoscopy
[g] count > 20 x 10^6/mL
[h] motility > 40%
[i] morphology > 50%
[y] "normal"
[z] not stated

Figure 5.1 Controlled Studies Comparing hMG plus IUI with hMG Alone in Women with Unexplained Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Obser-vations	Total	Obser-vations	Total		Lo	Hi	
1/3/2/2	Crosignani	1991	36	158	9	78	2.26	0.975	5.39	0.0061
1/1/1/2	Evans	1991	2	16	1	26	3.57	0.22	110	0.663
0/3/2/2	Serhal	1988	6	15	3	25	4.89	0.81	32.6	0.101
Common odds ratio and 95% CI							2.65	1.34	5.26	0.0061

Breslow-Day = 0.79, p = 0.94

* p value based on M-H corrected chi-square

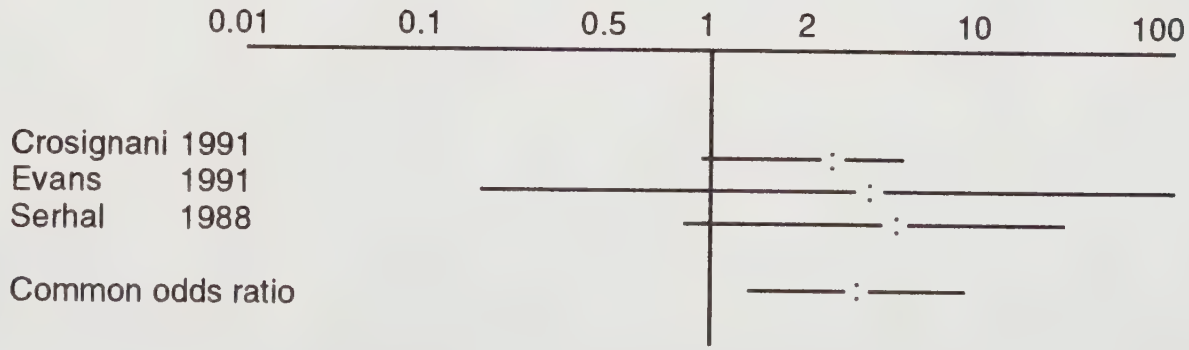


Table 5.2 Controlled Studies Comparing hMG ± IUI with IUI Alone or Intercourse Alone in Couples with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Nulsen 1990 3/3/2/2	Random allocation, method not described	32 (32)	32 (32)	Type infertility[b] Ovulation — endobiopsy Tubal status[e] (+[f] in rest) Sperm[y] Post-coital test[y]	hMG + IUI	IUI alone	Pregnancy	Two to three treatment cycles	Abstract only Crossover design Data not separable for first cycle
Welner 1988 0/3/2/2	Prospective cohort	97 (97) patients	48 (48)	Unexplained infertility + surgically corrected tubal disease and endometriosis with ≥1 patent tube	hMG two ampoules beginning cycle day 3	No active treatment	Pregnancy; miscarriage; endocrine response to hMG	Four treatment cycles of hMG versus approximately 6 months of observation in no-treatment groups	Pregnancy rates were reported per couple, not per cycle Sixty percent of couples had previously undergone tubal/pelvic surgery

Table 5.2 (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Serhal 1988 0/3/2/2	Retrospective cohort	49 (49) cycles	30 (30)	Type infertility[b] Ovulation[cd] Tubal status[f] Sperm[ghi] Post-coital test[y]	hMG three ampoules daily beginning day 2-3 ± IUI	IUI alone	Pregnancy	Study period only 1-2 cycles per couple	Results reported per patient and per cycle
Daly 1989 0/1/1/1	Prospective cohort	25 (?) patients	84 (?)	Type infertility[b] Ovulation[c] Tubal status[e] or [f] Sperm[gh] Post-coital test[y]	hMG ± IUI	No treatment	Pregnancy (viable)	Up to 17 months	Cohorts selected based on patient choice Significant difference in age — those choosing treatment: mean = 34.1, control = 31.4

[b] primary or secondary
[c] basal body temperature chart
[d] luteal serum progesterone
[e] HSG
[f] laparoscopy
[g] count > 20 x 10^6/mL
[h] motility > 40%
[i] morphology > 50%
[y] "normal"

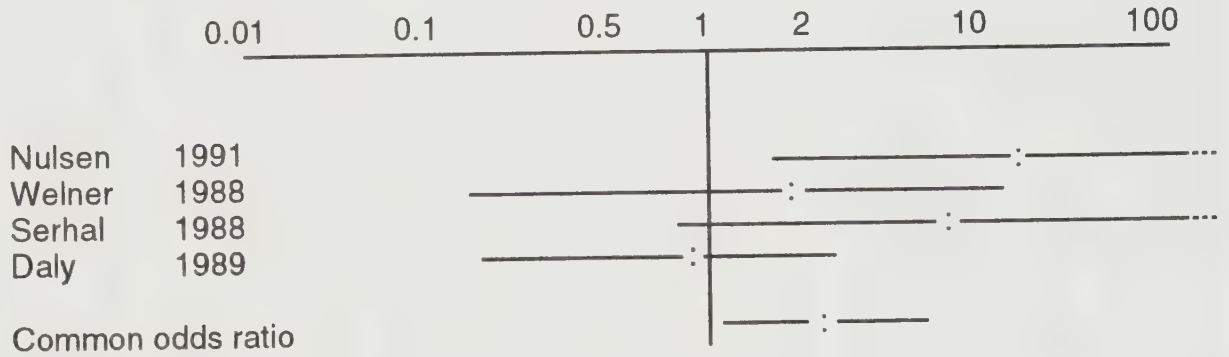
Figure 5.2 Controlled Studies Comparing Ovarian Hyperstimulation (hMG) plus IUI with No Treatment or IUI Alone in Women with Unexplained Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/1/1/2	Nulsen	1990	9	32	0	25	20.6	1.62	999	0.012
0/3/2/2	Welner	1988	3	39	2	48	1.92	0.242	17.5	0.057
0/3/2/2	Serhal	1988	6	15	1	15	9.83	0.82	243	0.090
0/1/1/1	Daly	1989	8	20	20	47	0.90	0.275	2.96	0.939
Common odds ratio and 95% CI							2.45	1.17	5.14	0.03

Breslow-Day = 8.78, p = 0.03

* p value based on M-H corrected chi-square



Overview Number: 6 (Table 6, Figure 6)

Title: **IVF Versus GIFT in Unexplained Infertility**

Editors: E.G. Hughes, J.A. Collins

Editorial Commentary

1. **Objective**: To determine the efficacy of IVF versus GIFT in unexplained infertility.
2. **Inclusion criteria for trials in this overview**: Randomized controlled studies of IVF versus GIFT were reviewed. Because of a paucity of data, cohort studies were also considered.
3. **Trials excluded**: None.
4. **Trials included**: Random or quasi-random allocation: Leeton et al. (1987); Crosignani et al. (1991). Cohort studies: Yovich and Matson (1988); Medical Research International (MRI) et al. (1991).
5. **Unpublished data**: None identified.
6. **Methodological quality**: The multicentre European study of Crosignani et al. (1991) used an unspecified form of randomization and a crossover design, but reported data separately from first and second treatment cycles. The quasi-randomized study of Leeton et al. (1987) used treatment allocation by alternate patient and had an extremely small sample size. The two cohort studies cited collected data from either multiple centres in 1989 (MRI et al. 1991) or from the same centre over a five-year period (Yovich and Matson 1988). Neither gave data describing the population demographics or a definition of unexplained infertility.
7. **Results**: Neither randomized trial comparing IVF with GIFT showed significant differences between treatments in this population. The common odds ratio was 0.85 (95% CI 0.487-1.49). When data from the two cohort studies were included, IVF appeared inferior to GIFT — common odds ratio 0.635 (95% CI 0.476-0.847, $p = 0.002$).
8. **Consistency of results across trials**: There was no statistically significant heterogeneity among the studies. Differences between populations are highly likely in both cohort studies.
9. **Risks and costs**: The maternal risks of IVF include moderate to severe ovarian hyperstimulation (approximately 1-3%) and the potential for injury to a viscus, during oocyte retrieval, or pelvic infection during the post-operative period. Significant complications such as these follow less than 1% of retrievals. Fetal risks include prematurity following multiple pregnancy (Fertility Society of Australia 1990). Perinatal mortality may even be increased in singleton IVF/GIFT pregnancies, though the data are conflicting (Fertility

Society of Australia 1990; Medical Research Council 1990). Treatment costs are approximately $2 000-$4 000 per cycle.

10. **Implications for practice**: Randomized controlled trials have demonstrated no significant difference between IVF and GIFT in the treatment of unexplained infertility. However, their power may have been insufficient to demonstrate small but clinically significant differences. Although cohort studies suggest that GIFT may be superior in this patient group, their validity is questionable.

11. **Implications for research**: In reporting data from cohort studies, more attention should be paid to potentially confounding variables such as age, parity, and duration of infertility. Logistic regression would be a useful tool in assessing their relative importance. Randomized trials in this area will be difficult to conduct because of the conventional wisdom that now favours GIFT.

12. **Conclusions**: The best available evidence suggests no difference between IVF and GIFT in the treatment of unexplained infertility.

Table 6. Controlled Trials Comparing IVF with GIFT in Couples with Unexplained Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Crosignani 1991 1/3/2/2	Random allocation, method not described	158 (158)	78 (78)	Type infertility[b] Ovulation[d] Tubal status[e] Sperm[ghi] < 38 years of age (female) > 3 years infertility Abstain from intercourse around treatment	IVF	GIFT	Pregnancy; spontaneous abortion	Two treatment cycles	Crossover trial with data given separately for first and second cycles
Leeton 1987 1/3/1/2	Quasi-random, alternate patients	49 (49)	37 (37)	Type infertility[z] Tubal status[f] Ovulation — endobiopsy Sperm[y]	IVF	GIFT	Pregnancy; spontaneous abortion	Study period only two cycles	Six patients switched from GIFT to IVF at time of laparoscopy Crossover trial

MRI 1991 0/?/?/?	Cohort study	247 (247) transfers	378 (378)	Unexplained infertility	IVF	GIFT	Pregnancy; live birth	Number of cycles per patient not reported	report of U.S. IVF statistics Multicentre
Yovich 1988 0/?/?/?	Cohort study	60 (60)	69 (69)	Unexplained infertility	IVF	GIFT	Pregnancy; spontaneous abortion	Number of cycles per patient not reported	Data from single centre over a 5-year period

[b] primary or secondary
[d] luteal serum progesterone
[e] HSG
[f] laparoscopy
[g] count > 20 x 10^6/mL
[h] motility > 40%
[i] morphology > 50%
[y] "normal"
[z] not stated

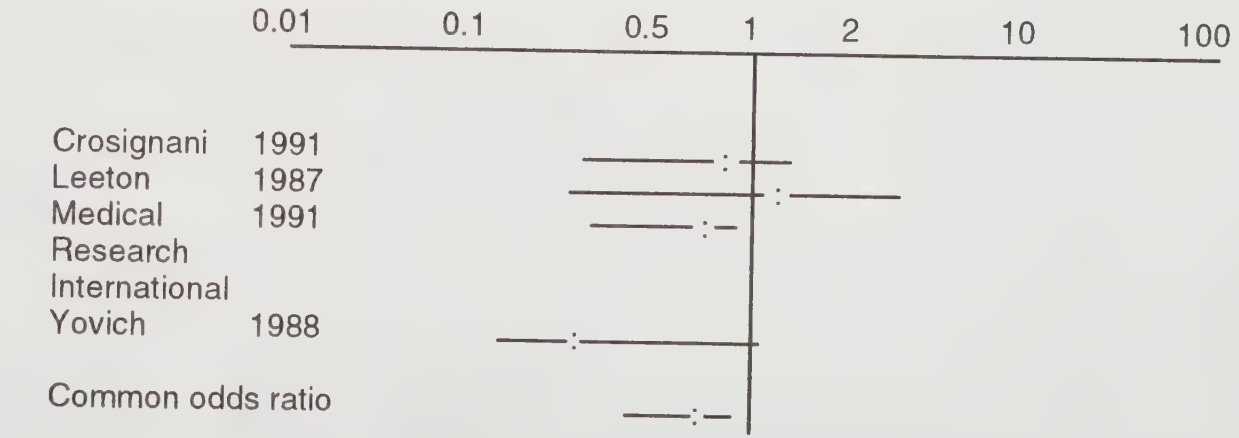
Figure 6. Controlled Trials Comparing IVF with GIFT in Couples with Unexplained Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental Obser-vations	Experimental Total	Control Obser-vations	Control Total	Odds ratio	95% CI Lo	95% CI Hi	p*
1/3/2/2	Crosignani	1991	77	37	114	0.78	0.39	1.47	0.55	0.55
1/3/1/2	Leeton	1987	37	7	49	1.16	0.35	4.37	0.95	0.95
0/?/?/?	MRI	1991	247	126	378	0.62	0.42	0.89	0.011	0.011
0/?/?/?	Yovich	1988	60	20	69	0.37	0.13	1.01	0.05	0.05
Common odds ratio and 95% CI						0.64	0.48	0.85	0.002	0.66

Breslow-Day = 2.74, p = 0.434

* p value based on M-H corrected chi-square



Summary and Conclusions

A number of empirical treatments for unexplained infertility have been evaluated through randomized controlled trials. There is no sound evidence to support the use of bromocriptine, Danazol®, or IUI in the treatment of unexplained infertility.

CC has been examined most carefully, and the available evidence suggests a significant treatment benefit, the common odds ratio for pregnancy being 2.6 (95% CI 1.49-4.54). Because of its relatively low cost and limited risks, this should be used as a primary therapy in couples requesting treatment.

The trials assessing the efficacy of gonadotropin plus IUI are less rigorous. Though a positive treatment effect may exist (common odds ratio = 2.65, 95% CI 1.34-5.26), this treatment approach is relatively expensive and carries significant risks of multiple pregnancy and ovarian hyperstimulation. Because the quantity and quality of data on this intervention are limited, the overall treatment benefit should be viewed with caution. Additional well-designed trials are needed, therefore, to assess its efficacy.

The limited data from randomized controlled trials comparing IVF and GIFT for the treatment of unexplained infertility demonstrated no significant difference between these approaches. Although cohort studies suggest that GIFT is superior in terms of ongoing pregnancy and live birth, without information describing the patients undergoing treatment, these data should be viewed with caution. More detailed reporting of registry data, using logistic regression in analyses, will help to answer this therapeutic question.

Part 2. Controlled Trials in Endometriosis-Related Infertility

Introduction

Endometriosis is the presence of endometrial tissue (glands and stroma) in sites other than the uterine cavity. The lesions are extremely variable when visualized with the naked eye. They range from a single spot in a pelvis that otherwise appears healthy to total pelvic disorganization by dense scar tissue formation.

The most comprehensive and widely accepted classification from the American Fertility Society (AFS) recognizes four stages ranging from minimal to severe. Numerical values are assigned to the findings within these groups. It is widely accepted that endometriosis of sufficient severity to cause pelvic disorganization (Stages III and IV) impairs fertility by

interfering with oocyte pickup and transport. The association is less clear in Stage I (minimal) and Stage II (mild) endometriosis. Although it has been recognized that endometriosis is more prevalent in women who have not borne children, it is unclear if minimal or mild endometriosis causes infertility or if childlessness simply allows the development of endometriotic lesions.

Although the etiology of endometriosis is unknown, several theories exist. The main theories are the implantation of endometrial fragments exposed to the pelvis by retrograde menstruation (Sampson 1927), metaplasia of celomic cells (Meyer 1919), and haematogenous and/or lymphatic spread (Sampson 1925). More recently, the development of endometriosis has been linked to a defect in the immunological system.

Neither the incidence (annual occurrence) nor the prevalence (proportion of the population affected) of endometriosis is known. Estimates have ranged from 1 to 50% (Schweppe 1988). The minimal standard for diagnosis is the direct visualization of lesions at the time of laparoscopy or laparotomy (Yuzpe and Taylor 1986). The invasive nature of the diagnostic test makes population-based incidence and prevalence studies impossible.

Despite the lack of clear causation, the observation of endometriosis in women with infertility has led to the advocation of numerous therapies. The overviews that follow attempt to evaluate the efficacy of treating endometriosis-related infertility.

Protocol for Meta-Analyses in Endometriosis-Related Infertility

Research Questions

In endometriosis-related infertility, do commonly used treatments enhance the rate of conception?

Population: Couples experiencing infertility associated with a laparoscopic diagnosis of endometriosis.

Interventions: Danazol®, medroxy progesterone, gonadotropin-releasing hormone (Gn-RH) analogues, laparoscopic laser or cautery, and conservative laparotomy.

Primary Outcome: Clinical pregnancy defined by a positive pregnancy test.

Study Identification

Studies were identified using the following search strategies:

1. The National Library of Medicine MEDLINE data base was accessed for the period 1966-1991 using the medical subject

headings "endometriosis," "infertility (female)," "pregnancy," and "therapy."

2. The Institute for Scientific Information Science Citation Index was explored for the period January 1986 - December 1989.
3. Additional studies were identified through bibliographies in existing review articles and from abstracts presented at scientific meetings.
4. Individual authors were contacted directly when necessary for further information.

This search strategy yielded a total of 114 references.

Inclusion Criteria

1. Population and interventions as described.
2. Methodology: Randomized controlled trials and cohort studies reporting a measurement of fecundity in two or more treatment arms have been included.

Validity Criteria Score

The greatest threat to the validity of these studies is the quality of treatment allocation. This is especially true in that the majority of studies used a non-randomized design. Identified studies were exposed to a 15-point methodological scale to quantify their quality (Table A). The methodological assessment was completed independently by two investigators. Agreement assessment between the two observers was accomplished using Cohen's kappa statistic, which yielded a good inter-observer correlation of 0.77.

Inter-observer differences were reviewed jointly, and all articles with differences of two or more points were re-examined. In all cases, observer error was the cause of major differences in scoring. Differences were resolved by consensus. The mean methodological assessment scores of the reviewed studies are presented in Table B. Only 13% of the studies achieved scores of greater than 10 out of a possible 15. The high number of studies with scores of less than five demonstrates that the existing methodological quality is quite variable. Overviews have been presented to allow visualization of the treatment effect, ranked by the methodological quality of the research.

Table A. Methodological Assessment for Studies of Treatment of Endometriosis-Related Infertility

Random or cohort	Random	2	Secondary infertility	Yes	1
	Cohort	0	is reported	No	0
Randomized: methods to reduce bias	Remote	2	Female age is reported	Yes	1
	Local	1		No	0
	Other	0			
Primary outcome is pregnancy	Yes	1	Follow-up loss is reported	Yes	1
	No	0		No	0
Includes placebo or untreated group	Yes	1	Loss to follow-up is less than 25%	Yes	1
	No	0		No	0
Current stage class used	Yes	1	Follow-up is more than 1 year	Yes	1
	No	0		No	0
Avoidance measures for bias in cohort studies are detailed	Yes	0	Prognostic variables reported by group	Yes	1
	No	−1		No	0
Duration of infertility is reported	Yes	1	Explicitly excludes other infertility diagnoses	Yes	1
	No	0		No	0

Table B. Mean Methodological Assessment Scores of Two Independent Observers of Reviewed Studies

Author	Design	Mean score (out of 15)
Badawy et al. (1988)	Cohort	6
Bayer et al. (1988)	Randomized controlled trial	11
Buttram et al. (1985)	Cohort	3.5
Chong et al. (1990)	Cohort	4.5
Dmowski et al. (1989)	Randomized controlled trial	6
Fayez et al. (1988)	Cohort	5
Fedele et al. (1989a)	Randomized controlled trial	11
Fedele et al. (1989b)	Randomized controlled trial	9.5
Federici et al. (1988)	Cohort	4.5
Garcia & David (1977)	Cohort	6
Guzick & Rock (1983)	Cohort	7.5
Henzl et al. (1988)	Randomized controlled trial	6.5
Hull et al. (1987)	Cohort	7

Table B. (*cont'd*)

Author	Design	Mean score (out of 15)
Levinson (1989)	Cohort	8
Noble & Letchworth (1979)	Randomized controlled trial	3
Nowroozi et al. (1987)	Randomized controlled trial	5
Olive & Lee (1986)	Cohort	3.5
Pouly et al. (1987)	Cohort	3.5
Ronnberg & Jarvinen (1984)	Cohort	6
Schenken & Malinak (1982)	Cohort	9
Seiler et al. (1986)	Cohort	2.5
Telimaa (1988)	Randomized controlled trial	10.5
Thomas & Cooke (1987)	Randomized controlled trial	13

Data Extraction

Data were extracted on the clinical characteristics of the patient's method of treatment, study design, and pregnancy rate for each selected study. Individual studies containing multiple treatment arms were considered to be independent two-armed assessments with the treatment group compared with the placebo or no-treatment arm. This resulted in a total of 33 treatment comparisons as indicated in Table C. Although this approach risks compromising the independence of the results of the 10 multiple treatment arms studied, only two contained two comparisons in a single overview (Hull et al. 1987; Telimaa 1988). The remaining nine studies generated only one comparison in a given overview.

Table C. Number of Identified Treatment Arms in Each Subgroup

	Randomized controlled trial	Cohort	Total
Ovulation suppression	9	5	14
Laparoscopic surgery	1	4	5
Laparoscopic surgery with Danazol®		5	5
Open laparotomy		5	5
Open laparotomy with Danazol®		4	4

Data Analysis

Common odds ratios were generated using the Mantel-Haenszel method as reported in the overviews dealing with unexplained infertility (Mantel and Haenszel 1959).

Overview Number: 7 (Tables 7.1 and 7.2, Figures 7.1 and 7.2)

Title: **Ovulation Suppression in the Infertility-Directed Treatment of Endometriosis**

Editors: D.M. Fedorkow, J.A. Collins, E.G. Hughes

Parts of this overview:

1. Ovulation suppression versus placebo
2. Ovulation suppression versus Danazol®

Editorial Commentary

1. **Objective**: To determine the efficacy of ovulation suppression in the treatment of endometriosis-associated infertility.
2. **Rationale**: The rationale behind ovulation suppression as a treatment for endometriosis-associated infertility is that the creation of a hormonal milieu less than ideal for the maintenance of ectopic endometrium will result in the regression and resorption of implants, thereby enhancing fecundity. The term "ovulation suppression" is used in this overview to describe all agents that impair ovarian steroidogenesis. Danazol® has become the accepted standard by which others are judged. A recent overview by Chan and Collins (1993) suggests that the use of Danazol® in the treatment of endometriosis-related infertility is similar in efficacy to placebo or no treatment at all. This overview, therefore, has been separated into two parts: one dealing with studies comparing an ovulation suppression agent with placebo or no treatment, and the other dealing with studies comparing ovulation suppression with active control through the use of Danazol®.
3. **Inclusion criteria for trials in this overview**: Randomized controlled trials and cohort studies comparing ovulation suppression agents with placebo, no treatment, or Danazol® were included.
4. **Trials included:** *Part 1.* Randomized controlled trials: Thomas and Cooke (1987); Bayer et al. (1988); Telimaa (1988). Cohort studies: Levinson (1989); Hull et al. (1987); Badawy et al. (1988); Pouly et al. (1987).

   Part 2. Randomized controlled trials: Fedele et al. (1989a, 1989b); Henzl et al. (1988); Dmowski et al. (1989); Noble and Letchworth (1979).

5. **Unpublished data:** Original data were solicited from one article (Levinson 1989).

6. **Methodological quality:** *Part 1.* Of the three randomized studies (four treatment arms), only the study by Bayer et al. (1988) describes its method of randomization (randomly numbered cards). None of the randomized trials uses a crossover design, and co-intervention does not appear to be present. Two studies explicitly excluded other infertility diagnoses from their patient sample (Thomas and Cooke 1987; Badawy et al. 1988). None of the retrospective cohort studies addressed possible co-intervention or contamination factors. As revealed by the methodological scores, only three studies (four treatment arms) yielded scores in excess of 10 out of 15.

   Part 2. Of the five randomized trials comparing two methods of ovulation suppression (using Danazol® as the control), only one obtained a mean methodological score greater than 10 (Fedele et al. 1989a). One trial described the method of randomization (Henzl et al. 1988). None of the studies used a crossover design. Co-intervention with clomiphene and other infertility treatments was a concern in three studies (Dmowski et al. 1989; Fedele et al. 1989a, 1989b). Contamination may have been an issue, as none of the studies explicitly excluded other infertility diagnoses. If this were the case, the true effect of treatment should have been stronger than that observed.

7. **Results:** *Part 1.* The results of these studies are weakly positive or weakly negative. All studies have 95% confidence intervals that include unity, the common odds ratio for this overview being 0.85 (95% CI 0.59-1.22). This suggests no significant treatment benefit for ovulation suppression over no treatment.

   Part 2. As in Part 1, all trials yielded weakly positive or weakly negative odds ratios. The combined odds ratio of 0.98 (95% CI 0.60-1.60) suggests no significant treatment effect of other ovulation suppression agents when compared with Danazol®.

8. **Consistency of results across trials:** The Breslow-Day test for heterogeneity yielded a value of 3.20 ($p = 0.92$) in Part 1 and a value of 2.18 ($p = 0.70$) in Part 2, suggesting no statistically significant heterogeneity between the studies.

9. **Implications for practice:** The use of ovulation suppression agents does not appear to confer any significant improvement in the treament of endometriosis-associated infertility.

10. **Implications for research:** Larger trials do not appear to be warranted based on these findings.

11. **Implications for remaining overviews:** Danazol® has long been accepted as the treatment of choice for endometriosis-associated infertility. It has therefore been used as an "active control" in studies

comparing treatment modalities. The results of this overview are in consort with the conclusion of Chan and Collins (1993) that the use of Danazol® in the treatment of endometriosis-related infertility is similar in efficacy to placebo or no treatment at all. The remaining overviews in this report, therefore, have combined data from studies including Danazol® as an "active control" with those from placebo or no-treatment control groups.

12. **Conclusions:** Ovulation suppression agents do not confer benefit to patients with endometriosis-associated infertility.

Table 7.1 Controlled Trials Comparing Ovulation Suppression with Placebo/No Treatment

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Thomas 1987 13	Randomization, double-blind controlled trial	20 (20)	20 (17)	Type infertility[b] Ovulation[c] Tubal status[e] and f Sperm[y] ≥ 1 year infertility	Gestrinone 2.5 mg twice weekly for 24 weeks	Placebo one tablet twice weekly for 24 weeks	Clinical pregnancy	12 months post-treatment	Excluded other causes Cumulative conception rates reported
Bayer 1988 11	Random allocation by "random card"	37 (37)	36 (36)	Ovulation[c] Tubal status[e] and f Sperm[y] ≥ 1 year infertility Endometriosis on laparoscopy	Danazol® 400-800 mg daily for 6 months	No treatment	Clinical pregnancy	12 months post-treatment	Life-table analysis reported

Table 7.1 (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Telimaa 1988 10.5	Random allocation, method not described	18 (18)	14 (14)	Endometriosis on laparoscopy Infertility duration unspecified	Danazol® 600 mg daily for 6 months	Placebo daily for 6 months	Clinical pregnancy	Up to 30 months post-treatment	Three-arm trial
Telimaa 1988 10.5	Random allocation, method not described	17 (17)	14 (14)	Endometriosis on laparoscopy Infertility duration unspecified	Provera 600 mg daily for 6 months	Placebo daily for 6 months	Clinical pregnancy	Up to 30 months post-treatment	Three-arm trial
Levinson 1989 8	Cohort	41 (41)	21 (21)	Infertility duration unspecified	Danazol® dose not reported	No treatment	Clinical pregnancy	12 months post-treatment	Minimal/mild endometriosis — AFS Stage I
Hull 1987 7	Cohort	52 (52)	56 (56)	Ovulation[c] Tubal status[e or f] Sperm[y] Infertility	Danazol® 600-800 mg daily for 6 months	No treatment	Clinical pregnancy	18-30 months post-treatment	AFS Stage I or II only

Hull 1987 7	Cohort	36 (36)	56 (56)	Ovulation Tubal status[e] and [f] Sperm[y]	10 mg three times daily (TID) for 90 d	treatment	pregnancy	30 months post-treatment	or II
Badawy 1988 6	Cohort	38 (38)	9 (14)	Ovulation[c] Tubal status[e] and [f] Sperm[y] Infertility duration unspecified	Danazol® 800 mg daily for 6 months	No treatment	Clinical pregnancy	1-5 years	—
Pouly 1987 3.5	Cohort	10 (10)	7 (7)	Tubal status[e] and [f] Sperm[y] ≥ 2 years infertility	Danazol®	No treatment	Clinical pregnancy	14 to 57-month follow-up	Selected 52 of possible 127 patients

[b] primary or secondary
[c] basal body temperature chart
[e] HSG
[f] laparoscopy
[y] "normal"

Figure 7.1 Controlled Trials Comparing Ovulation Suppression with No Treatment in the Treatment of Endometriosis-Associated Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI	
Validity score	1st author	Year	Observations	Total	Observations	Total	Odds ratio	Lo	Hi
13	Thomas	1987	5	20	4	17	1.08	0.17	5.62
11	Bayer	1988	13	37	17	36	0.61	0.21	1.73
10.5	Telimaa	1988	6	18	6	14	0.67	0.11	3.40
10.5	Telimaa	1988	7	17	6	14	0.93	0.16	4.59
8	Levinson	1989	17	41	9	21	0.94	0.28	3.02
7	Hull	1987	18	52	21	56	0.88	0.37	2.08
7	Hull	1987	16	36	21	56	1.33	0.52	3.34
6	Badawy	1988	16	38	9	14	0.40	0.08	1.75
3.5	Pouly	1987	4	10	3	7	0.89	0.04	7.83
Common odds ratio and 95% CI							0.85	0.59	1.22

Breslow-Day = 3.20, p = 0.92

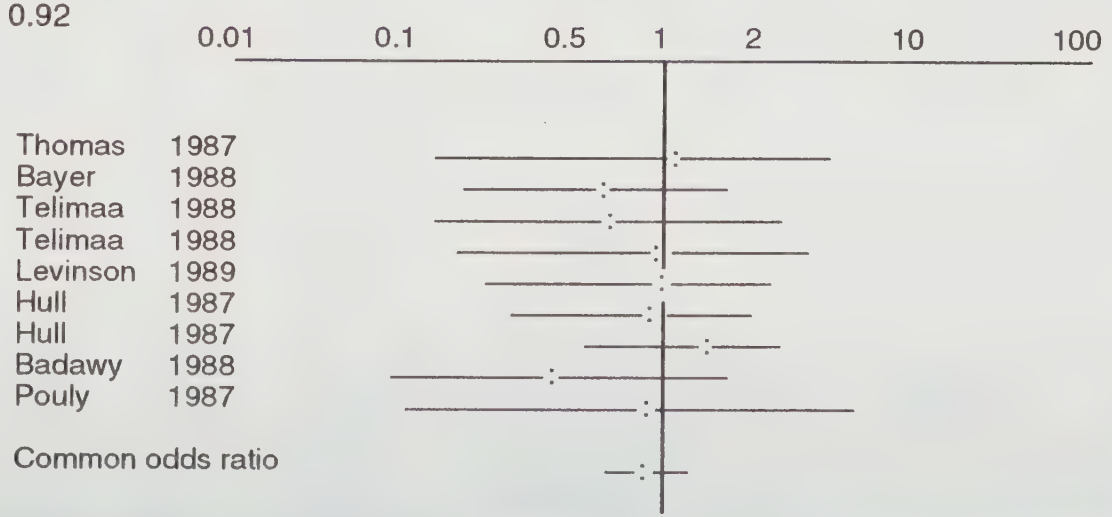


Table 7.2 Randomized Controlled Trials Comparing Ovulation Suppression with Danazol®

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Fedele 1989a 11	Random allocation, method not described	20 (19)	19 (19)	Type infertility[a] Ovulation[c] Tubal status[e] and f Sperm[y] Post-coital test[y]	Gastrinone 2.5 mg weekly for 6 months	Danazol® 600 mg daily for 6 months	Clinical pregnancy	18 months post-treatment	Bilateral tubal occlusion excluded Danazol® in preceding 6 months excluded
Fedele 1989b 9.5	Random allocation, method not described	30 (30)	32 (32)	Type infertility[a] Ovulation[c] Tubal status[e] and f Sperm[y] Post-coital test[y]	Buserelin 600 µg daily for 6 months	Danazol® 600 mg daily for 6 months	Clinical pregnancy	12 months post-treatment	Bilateral tubal occlusion excluded Danazol® in preceding 6 months excluded

Table 7.2 (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Henzl 1988 6.5	Double-blind, randomized controlled trial, central treatment allocation	104 (104)	45 (45)	Type infertility[b] Endometriosis on laparoscopy Infertility duration unspecified	Nafarelin 400-800 µg daily for 6 months	Danazol® 800 mg daily for 6 months	Clinical pregnancy	12 months post-treatment	Did not exclude other causes of infertility No hormonal treatment for 6 months before the study No surgical intervention
Dmowski 1989 6	Random allocation, method not described	? (18)	? (8)	Endometriosis on laparoscopy Infertility duration unspecified	Buserelin subcutaneous (SC) or intranasal (IN) 0.2-1.2 mg daily	Danazol® 800 mg daily for 6 months	Clinical pregnancy	12 months post-treatment	Did not exclude other causes No hormonal treatment for more than 8 months before enrolment

Nobel 1979 3	Random allocation, method not described	60 (10)	12 (12)	Endometriosis on laparoscopy Infertility duration unspecified	Enovid two tablets daily for 6 months	Danazol 400-800 mg daily for 6 months	Clinical pregnancy	exclude other causes

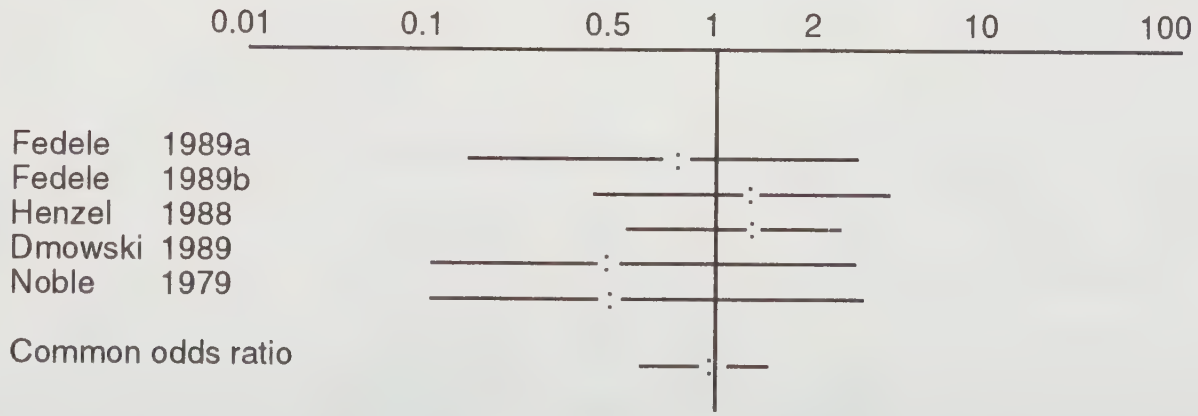
[a] primary
[b] primary or secondary
[c] basal body temperature chart
[e] HSG
[f] laparoscopy
[y] "normal"

Figure 7.2 Randomized Controlled Trials Comparing Ovulation Suppression with Danazol® in the Treatment of Endometriosis-Associated Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI	
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi
11	Fedele	1989a	6	20	7	19	0.73	0.16	3.39
9.5	Fedele	1989b	13	30	12	32	1.27	0.41	3.99
6.5	Henzl	1988	42	104	16	45	1.23	0.56	2.70
6	Dmowski	1989	8	18	5	8	0.48	0.06	3.48
3	Noble	1979	4	10	7	12	0.48	0.06	3.56
Common odds ratio and 95% CI							0.98	0.60	1.60

Breslow-Day = 2.18, p = 0.70



Overview Number: 8 (Table 8, Figure 8)

Title: **Laparoscopic Surgery in the Treatment of Endometriosis-Associated Infertility**

Editors: D.M. Fedorkow, J.A. Collins, E.G. Hughes

Editorial Commentary

1. **Objective**: To determine the effect of surgical ablation of endometriosis via the laparoscope in the treatment of endometriosis-associated infertility.
2. **Rationale**: Laparoscopic surgery, as a therapeutic modality, is gaining popularity. Treatment of endometriotic implants by laparoscopy involves their excision, coagulation, and/or laser vaporization. The premise is that the elimination of these lesions will enhance fecundity.
3. **Inclusion criteria for trials in this overview**: Studies comparing laparoscopic surgery with no treatment or treatment with Danazol® in the infertility-directed treatment of endometriosis.
4. **Trials included**: Quasi-randomized controlled trials: Nowroozi et al. (1987). Cohort studies: Levinson (1989); Fayez et al. (1988); Chong et al. (1990); Seiler et al. (1986).
5. **Unpublished data**: None identified.
6. **Methodological quality**: No identified study had a mean methodological score greater than 10. Only the study by Nowroozi et al. (1987) explicitly excluded patients with other infertility diagnoses. Co-intervention is not specifically addressed. The cohort studies are subject to bias, as the selection of treatment modalities may have been influenced by disease severity. The direction of such a bias is difficult to determine. It may be that patients with more extensive endometriosis were selected to receive Danazol® rather than laparoscopic surgery. This would favour surgery as a more effective treatment.
7. **Results**: Two of the five studies demonstrated significant benefit of laparoscopic destruction of endometriotic implants when compared with no treatment or the use of Danazol® (Nowroozi et al. 1987; Fayez et al. 1988). Combining the data yields a common odds ratio of 2.55 (95% CI 1.81-3.61), suggesting an increase in the clinical pregnancy rate in those patients treated with laparoscopic surgery.
8. **Consistency of results across trials**: The Breslow-Day test demonstrated a significant lack of homogeneity across the studies ($p = 0.000$). This is likely a reflection of the different patient groups represented in the studies. Because of these differences, the

combined effect should be interpreted with caution. This heterogeneity has the effect of artificially narrowing the 95% confidence interval generated from the common odds ratio.

9. **Implications for practice**: Because of the significant lack of homogeneity among the studies in this overview, the conclusion that laparoscopic surgery is efficacious in the treatment of endometriosis-related infertility cannot be made with confidence.

10. **Implications for research**: The apparent beneficial effect of laparoscopic surgery in the treatment of endometriosis-associated infertility deserves further study in large, well-controlled randomized trials.

11. **Conclusions**: The common odds ratio suggests that there may be a positive effect. Further investigation is warranted because of the limited quality and significant heterogeneity of the data.

Table 8. Controlled Trials Comparing Laparoscopic Laser/Cautery Surgery with Danazol® in the Treatment of Endometriosis-Associated Infertility

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Levinson 1989 8	Cohort	83 (83)	21 (21)	Infertility duration unspecified	Electrocautery via laparoscopy	Diagnostic laparoscopy	Clinical pregnancy	12 months post-treatment	Minimal/mild endometriosis AFS Stage I
Nowroozi 1987 5	Quasi-random by social security number	69 (69)	54 (54)	AFS Stage I, II Infertility	Electrocautery via laparascopy	Diagnostic laparoscopy	Clinical pregnancy	8 months	Co-intervention a major concern
Fayez 1988 5	Prospective cohort	172 (172)	76 (76)	AFS minimal or mild endometriosis ≥ 1 year infertility	Laparoscopic excision ± Danazol®	Danazol® 800 mg/d	Clinical pregnancy	12 months post-treatment	Allocation by time period of 18 months each

Table 8. (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Chong 1990 4.5	Retrospective cohort	83 (83)	47 (47)	R-AFS Stage I Revised American Fertility Society	Laser ± CO_2 Danazol® 600-800 mg/d for 4 months	Danazol® 600-800 mg/d for 6 months	Clinical pregnancy	12 months post-treatment	Other causes of infertility not excluded Laparoscopic surgery group older than others
Seiler 1986 2.5	Prospective cohort	45 (45)	45 (41)	Type infertility[b] Tubal status[f] "Moderate" endometriosis (Acosta 1973)	Electrocautery via laparoscopy with lysis of adhesions	Diagnosis laparoscopy	Clinical pregnancy	7 months post-treatment	Allocation by time periods of 2-3 months

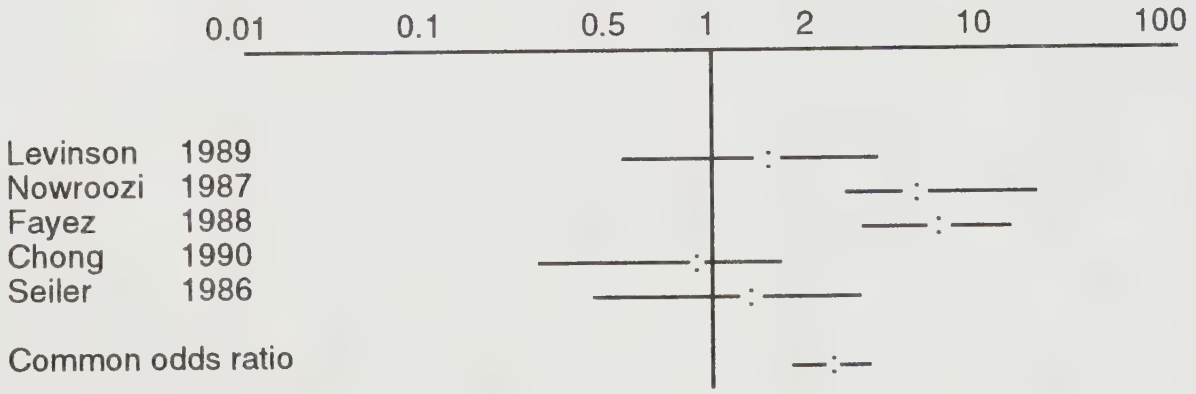
[b] primary or secondary
[f] laparoscopy

Figure 8. Controlled Trials Comparing Laparoscopic Laser/Cautery Surgery with No Treatment or Danazol® Alone in the Treatment of Endometriosis-Related Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI	
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi
8	Levinson	1989	44	83	9	21	1.50	0.52	4.40
5	Nowroozi	1987	42	69	10	54	6.84	2.75	17.40
5	Fayez	1988	60	82	20	76	7.63	3.56	16.56
4.5	Chong	1990	37	83	23	47	0.84	0.38	1.83
2.5	Seiler	1986	20	45	16	41	1.25	0.48	3.23
Common odds ratio and 95% CI							2.55	1.81	3.61

Breslow-Day = 28.33, p = 0.000



Overview Number: 9 (Table 9, Figure 9)

Title: **The Combination of Laparoscopic Surgery and Danazol® in the Treatment of Endometriosis-Related Infertility**

Editors: D.M. Fedorkow, J.A. Collins, E.G. Hughes

Editorial Commentary

1. **Objective**: To determine the efficacy of the combination of laparoscopic surgery and Danazol® in the treatment of endometriosis-associated infertility.
2. **Inclusion criteria for trials in this overview**: Studies comparing laparoscopic surgery with adjuvant Danazol® versus treatment with the active control Danazol® or no treatment form the basis of this overview.
3. **Trials included**: Levinson (1989); Ronnberg and Jarvinen (1984); Fayez et al. (1988); Chong et al. (1990); Pouly et al. (1987).
4. **Unpublished data**: Original data were solicited from one article (Levinson 1989).
5. **Methodological quality**: Five cohort studies were identified. The study by Pouly et al. (1987) used a no-treatment comparison group, whereas the other four studies compared the intervention with the active control Danazol®. No study received a mean methodological score greater than 10. All studies used a cohort design with the potential for selection bias in the choice of treatments. Such a selection bias may favour laparoscopic surgery, because patients with more advanced disease would have been less likely to have undergone this procedure. Alternatively, the selection bias may have resulted in preferential assignment to Danazol® therapy for those patients with less severe disease, as laparoscopic surgery might not have been considered to be valuable. Co-intervention may also be a factor because none of the studies explicitly excluded patients with other infertility diagnoses. This also introduces the potential for contamination.
6. **Results**: These studies reach different conclusions. Three studies fail to demonstrate a significant difference in the rate of clinical pregnancy between groups (Pouly et al. 1987; Levinson 1989; Chong et al. 1990). Ronnberg and Jarvinen (1984) showed a higher pregnancy rate in those patients receiving Danazol® alone than in those patients receiving a combination of laparoscopic surgery and Danazol®. Fayez et al. (1988), on the other hand, found a statistically significant increase in fecundity in the group that underwent surgery. The overview analysis failed to show a significant difference between the treatment groups — common odds ratio 1.42 (95% CI 0.94-2.14).

7. **Consistency of results across trials**: The Breslow-Day test shows a significant lack of homogeneity among the studies. As in the previous overview, this likely results from differences in the populations studied. As stated earlier, the effect of heterogeneity on the common odds ratio is an artificial narrowing of the 95% confidence interval. It is unlikely, therefore, that the lack of treatment effect found in this overview is secondary to heterogeneity.

8. **Implications for practice**: Currently available evidence does not favour laparoscopic surgery with adjuvant Danazol® over Danazol® alone or no treatment in the treatment of endometriosis-related infertility.

9. **Implications for research**: Well-designed studies addressing the issue are warranted before the effectiveness of the treatment can be addressed.

10. **Conclusions**: There is no evidence to support the use of laparoscopic surgery with adjuvant Danazol® in the treatment of endometriosis-related infertility. However, the methodological quality of existing evidence is poor and more definitive studies are needed to determine the effectiveness of this treatment.

Table 9. Controlled Trials Comparing Laparoscopic Surgery plus Danazol® with Danazol® Alone or No Treatment

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Levinson 1989 8	Cohort	44 (44)	21 (21)	Infertility duration unspecified	Electrocautery via laparoscopy	Diagnostic laparoscopy	Clinical pregnancy	12 months post-treatment	Minimal/mild endometriosis AFS Stage I
Ronnberg 1984 6	Cohort	18 (18)	59 + 4 (59 + 4)	Endometriosis on laparoscopy Infertility duration unspecified	Laparoscopic electrocautery + Danazol® 600 mg daily for 6 months post-operatively	Danazol® 600 mg/d for 6 months or no treatment	Clinical pregnancy	12 months post-treatment	Major differences between groups Milder disease in laparoscopic surgery or no treatment
Fayez 1988 5	Prospective cohort	80 (80)	76 (76)	AFS minimal or mild endometriosis ≥ 1 year infertility	Laparoscopic excision ± Danazol®	Danazol® 800 mg/d	Clinical pregnancy	12 months post-treatment	Allocation by time period of 18 months each

Chong 1990 4.5	Retrospective cohort	(37)	(47)		Danazol® 600-800 mg/d for 4 months	600-800 mg/d for 6 months	pregnancy	post-treatment	of infertility not excluded Laparoscopic surgery group older than others
Pouly 1987 3.5	Cohort	29 (29)	10 (10)	Tubal status[e] and [f] Sperm[y] ≥ 2 years infertility	Danazol®	No treatment	Clinical pregnancy	14 to 57-month follow-up	Selected 52 of possible 127 patients

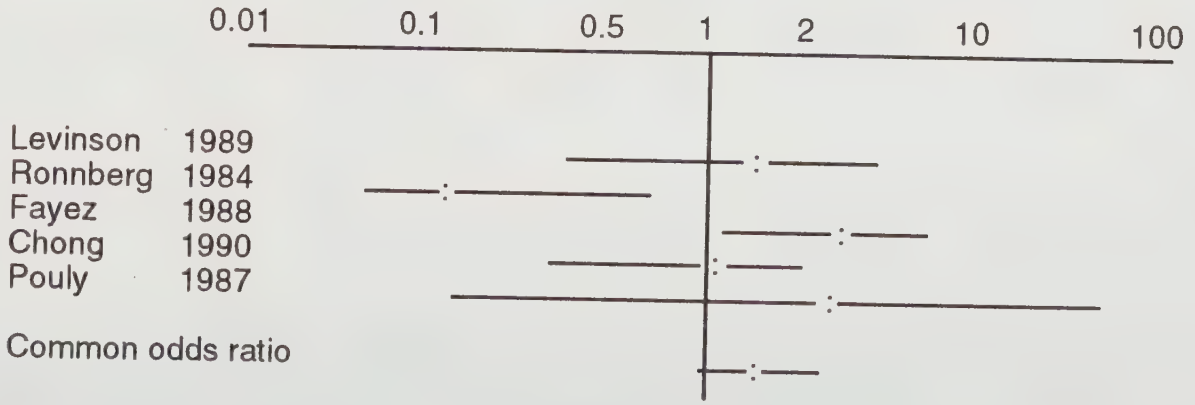
[e] HSG
[f] laparoscopy
[y] "normal"

Figure 9. Controlled Studies Comparing Laparoscopic Laser/Cautery Surgery plus Danazol® with No Treatment or Danazol® Alone in the Treatment of Endometriosis-Related Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI	
			Obser-vations	Total	Obser-vations	Total		Lo	Hi
8	Levinson	1989	23	44	9	21	1.46	0.45	4.75
6	Ronnberg	1984	3	18	33	63	0.16	0.03	0.67
5	Fayez	1988	43	80	20	76	3.25	1.56	6.77
4.5	Chong	1990	19	37	23	47	1.10	0.43	2.59
3.5	Pouly	1987	19	29	4	10	2.67	0.17	50.05
Common odds ratio and 95% CI							1.42	0.94	2.14

Breslow-Day = 19.35, p = 0.0007



Overview number: 10 (Table 10, Figure 10)

Title: **Conservative Laparotomy in the Infertility-Directed Treatment of Endometriosis**

Editors: D.M. Fedorkow, J.A. Collins, E.G. Hughes

Editorial Commentary

1. **Objective**: To determine the efficacy of conservative laparotomy compared with no treatment or Danazol® alone in the treatment of endometriosis-associated infertility.
2. **Rationale**: The goal of conservative surgery is to remove as much disease as possible, restore normal anatomy, and preserve fertility. It is assumed that by adopting these principles, fecundity can be enhanced.
3. **Inclusion criteria for trials in this overview**: Studies comparing conservative laparotomy with no treatment or Danazol® accessioned by the previously described strategy.
4. **Trials included**: Cohort studies with no-treatment control group: Schenken and Malinak (1982); Garcia and David (1977); Olive and Lee (1986). Cohort studies with Danazol® control group: Guzick and Rock (1983); Ronnberg and Jarvinen (1984).
5. **Unpublished data**: None identified.
6. **Methodological quality**: None of the studies had a methodological score greater than 10, and none explicitly excluded other infertility diagnoses. In addition, because these were all cohort studies, the potential for selection bias exists. This bias may have worked in different directions, as patients may have entered the no-surgery group because their disease was considered to be too advanced or too mild to warrant surgery. Co-intervention was not actively denied in any study. Ronnberg and Jarvinen (1984) included couples with other causes of infertility, which may have influenced the results generated.
7. **Results**: Three of the five studies failed to demonstrate a significant improvement in the clinical pregnancy rate between groups (Garcia and David 1977; Schenken and Malinak 1982; Ronnberg and Jarvinen 1984). The study by Olive and Lee (1986) demonstrated a statistically significant decrease in the clinical pregnancy rate in those patients treated by conservative laparotomy. The study by Garcia and David (1977) showed an increase in the crude pregnancy rate following conservative laparotomy, but no difference in the cumulative pregnancy rate. The common odds ratio for pregnancy of 1.06 (95% CI 0.77-1.45) does not support the hypothesis that conservative laparotomy is an effective means of restoring fertility in patients with endometriosis.

8. **Consistency of results across trials**: The Breslow-Day test demonstrates heterogeneity among the studies ($p = 0.000$). This heterogeneity, although demonstrating a lack of consistent treatment effect across the studies, does not explain the failure to demonstrate a treatment effect as described in the previous overview.
9. **Implications for practice**: Existing evidence does not support the use of conservative laparotomy in the infertility-directed treatment of endometriosis.
10. **Implications for research**: As with the previous overview, the methodological quality of existing data necessitates further investigation to conclusively comment on the effectiveness of conservative laparotomy in the infertility-directed treatment of endometriosis.
11. **Conclusions**: Currently available data do not support the use of conservative laparotomy in the infertility-directed treatment of endometriosis.

Table 10. Controlled Trials Comparing Laparotomy with No Treatment/Danazol®

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		Experimental	Control						
Schenken 1982 9	Cohort	42 (42)	18 (18)	Mild endometriosis ≥ 1 year infertility Ovulation[cd] Tubal status[e] Sperm[y]	Laparotomy	No treatment	Clinical pregnancy	> 12 months post-treatment	AFS Stages I and II Table and text numbers differ in surgery group
Guzick 1983 7.5	Cohort	133 (133)	91 (91)	Mild/moderate endometriosis Type infertility[b] ≥ 1 year infertility Ovulation (method not reported) Tubal status[e] and f Sperm[y]	Laparotomy	Danazol®	Clinical pregnancy	Up to 72 months	Patients with other forms of infertility excluded Surgical patients had longer follow-up

Table 10. (*cont'd*)

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experi-mental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experi-mental**	**Control**						
Ronnberg 1984 6	Cohort	90 (90)	59 + 4 (59 + 4)	Endometriosis on laparoscopy Infertility duration unspecified	Laparotomy	Danazol®	Clinical pregnancy	12-66 months	Major differences between groups Milder disease in laparoscopic surgery or no treatment
Garcia 1977 6	Cohort	71 (71)	43 (43)	Endometriosis on laparoscopy Infertility duration unspecified	Laparotomy	No treatment	Clinical pregnancy	Up to 60 months	
Olive 1986 3.5	Cohort	88 (88)	42 (42)	Infertility duration unspecified Ovulation[y] Tubal status[e] Sperm[y]	Surgery	No treatment	Clinical pregnancy	Up to 40 months	Life-table analysis also considered spontaneous pregnancy in the pre-surgical group

other forms of infertility

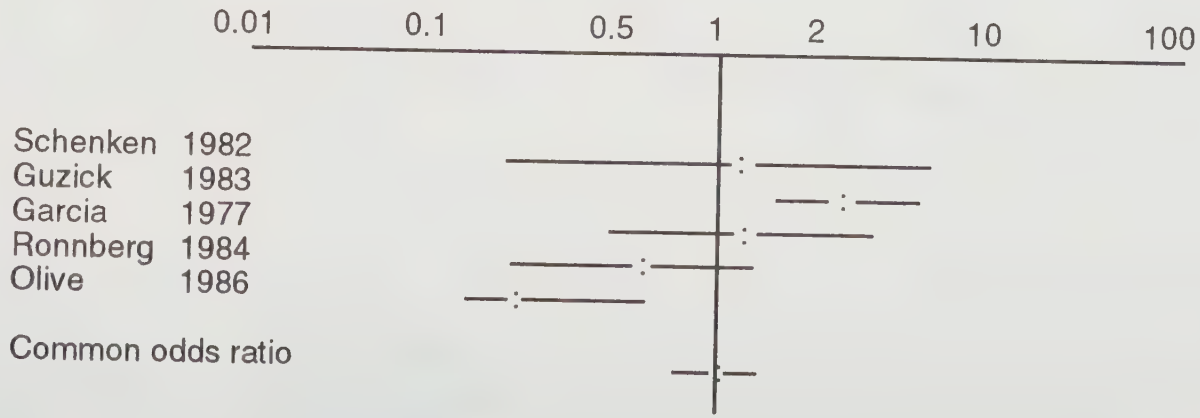
b	primary or secondary	e	HSG
c	basal body temperature chart	f	laparoscopy
d	luteal serum progesterone	y	"normal"

Figure 10. Controlled Trials Comparing Conservative Laparotomy with No Treatment or Danazol® Alone in the Treatment of Endometriosis-Associated Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI	
			Observations	Total	Observations	Total		Lo	Hi
9	Schenken	1982	32	42	13	18	1.23	0.29	5.03
7.5	Guzick	1983	76	133	30	91	2.75	1.52	5.01
6	Garcia	1977	23	71	12	43	1.23	0.50	3.09
6	Ronnberg	1984	39	90	33	59	0.60	0.29	1.23
3.5	Olive	1986	37	88	30	42	0.29	0.12	0.68
Common odds ratio and 95% CI							1.06	0.77	1.45

Breslow-Day = 25.42, p = 0.000



Overview Number: 11 (Table 11, Figure 11)

Title: **The Combination of Conservative Laparotomy and Danazol® in the Infertility-Directed Treatment of Endometriosis**

Editors: D.M. Fedorkow, J.A. Collins, E.G. Hughes

Editorial Commentary

1. **Objective**: To determine the efficacy of the combination of conservative laparotomy and Danazol® in the treatment of endometriosis-associated infertility.
2. **Inclusion criteria for trials in this overview**: Studies comparing conservative laparotomy with adjuvant Danazol® versus no treatment or Danazol® alone.
3. **Trials included**: Cohort study with a no-treatment comparison: Badawy et al. (1988). Cohort studies using Danazol® for comparison: Ronnberg and Jarvinen (1984); Federici et al. (1988); Buttram et al. (1985).
4. **Unpublished data**: None identified.
5. **Methodological quality**: All identified studies used a cohort design with the associated potential biases discussed in previous overviews. The highest methodological score recorded in this overview was six (Ronnberg and Jarvinen 1984; Badawy et al. 1988). No study explicitly excluded patients with other infertility diagnoses, thereby generating the potential for contamination and co-intervention.
6. **Results**: No study generated statistically significant results with all confidence intervals, including unity. The resultant common odds ratio of 1.01 (95% CI 0.67-1.52) fails to demonstrate a significantly improved clinical pregnancy rate with conservative laparotomy and Danazol®.
7. **Consistency of results across trials**: The Breslow-Day test suggests that there is a significant lack of homogeneity across the studies. As stated in the previous overviews, this heterogeneity is an unlikely explanation for the lack of observed treatment effect.
8. **Implications for practice**: Existing data fail to demonstrate the effectiveness of the combination of conservative laparotomy with adjuvant Danazol® in the infertility-directed treatment of endometriosis.
9. **Implications for research**: The poor methodological quality of the existing literature necessitates the performance of additional carefully designed research before the effectiveness of conservative laparotomy with adjuvant Danazol® can be determined.
10. **Conclusions**: Existing evidence does not support the efficacy of conservative laparotomy with adjuvant Danazol® in the infertility-directed treatment of endometriosis.

Table 11. Trials Comparing Conservative Laparotomy and Danazol® with No Treatment/Danazol®

1st author year	Method of allocation	Patients allocated (nos. included in analysis)		Entry criteria	Experi-mental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experi-mental**	**Control**						
Badawy 1988 6	Cohort	66 (66)	14 (14)	≥ 1 year infertility Ovulation[cd] Tubal status[ef] Sperm[y]	Pre-operative Danazol® and surgery	No treatment	Clinical pregnancy	1-58 months	Cumulative pregnancy rates reported
Ronnberg 1984 6	Cohort	44 (44)	59 (59)	Infertility duration unspecified	Danazol® and surgery	Danazol®	Clinical pregnancy	12-66 months	Milder disease in control group
Federici 1988 4.5	Cohort	29 (28)	120 (120)	Infertility duration unspecified	Danazol® and surgery	Danazol®	Clinical pregnancy	Not reported	Milder disease in control group Crude pregnancy rates only
Buttram 1985 3.5	Cohort	99 (99)	58 (58)	Infertility duration unspecified	Bromocriptine 2.5 mg BID 3 months	Danazol®	Clinical pregnancy		

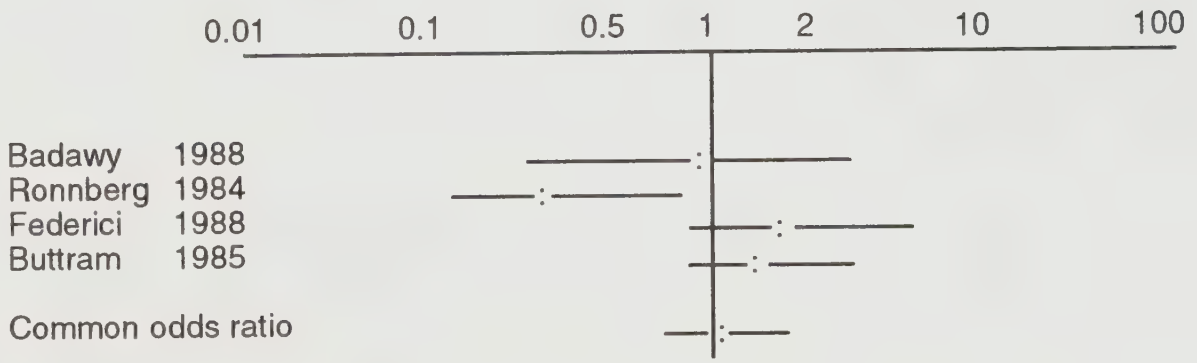
[c] basal body temperature chart
[d] luteal serum progesterone
[e] HSG
[f] laparoscopy
[y] "normal"

Figure 11. Controlled Trials Comparing Conservative Laparotomy and Danazol® with No Treatment or Danazol® Alone in the Treatment of Endometriosis-Associated Infertility: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI	
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi
6	Badawy	1988	42	66	9	14	0.97	0.30	3.20
6	Ronnberg	1984	14	44	33	59	0.38	0.18	0.83
4.5	Federici	1988	11	28	33	120	1.75	0.71	4.29
3.5	Buttram	1985	56	99	27	58	1.49	0.78	2.85
Common odds ratio and 95% CI							1.01	0.67	1.52

Breslow-Day = 8.885, p = 0.031



Summary and Conclusions

Existing data on treatments that may eliminate endometriosis do not demonstrate a beneficial effect on fecundity. All treatment groups, with the exception of laparoscopic ablation of endometrial implants, failed to demonstrate a beneficial effect of the treatment in terms of restoring fertility, with common odds ratios in all but one overview being close to one and with 95% confidence intervals including unity. The notable exception of laparoscopic laser or cautery surgery suffers from a small number of subjects and significant heterogeneity among studies, thereby raising questions regarding the validity of the overview results. This suggests that the treatment effect is not consistent across studies.

All overviews, with the exception of ovulation suppression compared with no treatment or treatment with Danazol®, demonstrated significant heterogeneity as measured by the Breslow-Day test. This suggests that there may exist significant differences in treatment effects across studies. This may represent a selection bias in the cohorts assembled.

These studies are not uniform in their treatment allocation and generally have small sample sizes. By combining the results, no specific benefit of treatment on the fecundity of couples suffering from endometriosis can be demonstrated. This is contrary to currently ingrained clinical opinion. One must conclude that, at present, it is not possible to recommend any particular treatment as being effective in restoring the fertility of patients with endometriosis.

It is evident that further investigations need to be completed. The significant heterogeneity among studies necessitates the adoption of large carefully controlled trials to address the different treatment regimes prior to definitively supporting the use of any of these regimens in the treatment of endometriosis-related infertility.

It can be concluded from the results of this overview that ovulation suppression confers no benefit on the infertility-directed treatment of endometriosis when compared with no treatment. Similarly, existing data do not support the effectiveness of conservative surgery with or without the adjuvant use of ovulation suppression in such treatment. The effect of laparoscopic ablation of endometrial implants is encouraging, but requires further evaluation before its use can be advocated with confidence.

Part 3. Controlled Trials in Assisted Reproductive Technology

Introduction

Although the literature on assisted reproduction is expanding rapidly, we are aware of only one trial comparing IVF with no treatment (Jarrell

et al. 1993). Results of this study were not available for appraisal at the time of writing. The following overviews, therefore, summarize randomized controlled trials comparing different components of assisted reproductive technologies. Groups of similar studies were identified in three main areas, and these have been subjected to formal meta-analysis. Single studies of more diverse interventions have not been included in the current report because their results could not be meaningfully pooled.

Protocol for Meta-Analyses in IVF and GIFT

Research Questions

In infertile couples undergoing *in vitro* fertilization-embryo transfer (IVF-ET) or GIFT, does the use of specific treatment protocols significantly improve the clinical pregnancy rate?

Interventions: Gonadotropin-releasing hormone agonist (Gn-RHa) versus traditional ovulation induction protocols, luteal support with hCG, and luteal support with progesterone.

Primary Outcome: Clinical pregnancy (evidence of pregnancy by ultrasound or by trophoblastic tissue following abortion). Data on live birth are rarely reported. As a surrogate for this endpoint, data on spontaneous abortion have been included, when available, to estimate rates of ongoing pregnancy.

Study Identification

1. Retrospective journal hand-search: Forty-one core journals have been hand-searched in collaboration with the Leeds University group from January 1980 to January 1990 using the following selection criteria: (a) randomized or quasi-randomized controlled trials; (b) therapeutic intervention in infertile couples; and (c) pregnancy, a defined and reported outcome.
2. Prospective hand-search beginning in January 1990: Forty-one core journals were prospectively hand-searched using the same selection criteria as described above.
3. Studies were identified through the National Library of Medicine MEDLINE data base from 1980 to the present using keywords.

   For all overviews, the following keywords were used: fertilization *in vitro* (medical subject heading [MeSH]); gamete intrafallopian transfer (MeSH); comparative study (MeSH); and random* (text word). Additional keywords were used for specific overview searches. For

* Random was used as a text word root allowing identification of words such as "randomization."

Gn-RH, for example, gonadorelin — analogues and derivatives (MeSH) was used.

4. Forward search with SCISEARCH data base: frequently cited articles were searched from 1986 to the present.
5. Letters to authors: Researchers producing relevant articles have been provided with a list of studies identified so far. Missing studies and unpublished data can then be identified.

Strategy for Study Retrieval

Independent authors have reviewed the MEDLINE search and hand-searches to determine which articles should be retrieved for evaluation and possible inclusion. As a pilot study to evaluate retrieval criteria, a sample of 50 citations was assessed and the level of agreement between two authors measured (kappa 0.72) for articles to be retrieved. All potentially relevant articles were photocopied and reviewed independently by at least two reviewers, using the selection criteria listed in each overview.

Inclusion Criteria

Articles were copied in full without blinding of the author to the journal. Methods sections of potentially relevant articles were reviewed independently. A pilot study of 15 manuscripts was used to assess the criteria for study inclusion in the Gn-RHa overview. Inter-observer agreement measured by kappa was 1.0. Differences of opinion were subsequently resolved by consensus.

Validity Criteria Score

The criteria used for validity assessment are listed below in order of attributed importance. The scores afforded each study appear below the first author's name in each table and figure.

1. Randomization procedure
   (a) randomized by central means (telephone or pharmacy)
   (b) randomized by sealed accounted envelope
   (c) randomization method other than above, method not described, or day of month, date of birth, or clinic chart number (quasi-randomization) used
2. Follow-up
   (a) outcome data used for primary analysis complete — all randomized patients accounted for, with "intention to treat" analysis

(b) outcome data incomplete, with < 5% of cycles commenced having outcome data missing

(c) outcome data incomplete, with > 5% of cycles commenced having outcome data missing

3. Patients and cycles differentiated?

(a) only included first treatment cycles

(b) number of patients and cycles stated separately; number of patients having repeat cycles reported

(c) number of patients and cycles not differentiated; cannot be certain whether some patients were treated more than one cycle

4. Co-intervention?

(a) other than for use of treatment and control, protocols for ovulation induction and luteal support were the same

(b) difference in protocol in addition to treatment versus control (difference stated if present)

Data Extraction and Analysis

Data extraction was accomplished using a pretested form. In all cases, data extraction has been checked for accuracy. The same principles were applied to data analysis as were reported in the overviews dealing with the treatment of unexplained infertility.

Overview Number: 12 (Tables 12.1 and 12.2, Figures 12.1-12.5)

Title: **Gn-RHa Versus CC/hMG/FSH Ovulation Induction Protocols in IVF and GIFT**

Editor: E.G. Hughes

Parts of this overview:

1. Cycle cancellation (10 trials)
2. IVF clinical pregnancy (10 trials)
3. GIFT clinical pregnancy (4 trials)
4. IVF clinical pregnancy, flare-up versus suppression regimes (5 trials)
5. Spontaneous abortion following IVF and GIFT (6 trials)

Editorial Commentary

1. **Objective**: To evaluate the efficacy of Gn-RHa-based ovulation induction protocols in infertile couples undergoing IVF and GIFT

compared with more traditional ovulation induction protocols, including CC/hMG, hMG alone, FSH/hMG, and FSH alone, using clinical pregnancy as the primary outcome.

2. **Inclusion criteria for trials in this overview**: Randomized and quasi-randomized trials comparing Gn-RHa ovulation induction protocols with other approaches. Also included were trials comparing short or "flare-up" Gn-RHa protocols (Gn-RHa commenced in conjunction with hMG in the follicular phase of a treatment cycle) with long or "suppression" protocols (Gn-RHa commenced in the luteal phase of the pre-treatment cycle).

3. **Trials excluded**: Belaisch-Allart et al. (1990); Salat-Baroux et al. (1988); Ron-El et al. (1990) — two similar types of suppression regime compared. Garcia et al. (1990); Edelstein et al. (1990); Lipitz et al. (1989); Dor et al. (1990); MacLachlan et al. (1989); Hassiakos et al. (1990); Benadiva et al. (1990); Chetkowski et al. (1989); Macnamee et al. (1989); Ashkenazi et al. (1989) — treatment allocation non-random.

4. **Trials included**: Thirteen trials have been identified that meet the criteria for this overview: Neveu et al. (1987); Gonen et al. (1991); Abdalla et al. (1990); Antoine et al. (1990); Ferrier et al. (1990); Kubik et al. (1990); Loumaye et al. (1989); Maroulis et al. (1991); Polson et al. (1991); Remorgida et al. (1989); Ron-El et al. (1991); van de-Helder et al. (1990); Dirnfeld et al. (1991).

5. **Unpublished data**: Authors of five included trials have responded to requests for further information (Remorgida et al. 1989; Antoine et al. 1990; Kubik et al. 1990; Maroulis et al. 1991; Polson et al. 1991). No further unpublished data have been identified.

6. **Methodological quality**: The greatest threat to the validity of these studies is the quality of randomization. Only one trial describes a "central" form of randomization (Polson et al. 1991). Through direct contact with the author, a trial using allocation by sealed envelope was also identified (Antoine et al. 1990). The remaining trials either do not report the method of randomization used or describe quasi-randomization by alternating days or patients.

   The other general concern involves differentiation between patients and treatment cycles. Only three studies considered first treatment cycles (Remorgida et al. 1989; Kubik et al. 1990; van de-Helder et al. 1990). In none of the remaining studies was it possible to extract data from a single cycle per patient.

   A final important factor is the possibility of "publication bias" (the selective publication of positive trials). An ongoing search for unpublished data continues through direct contact with authors.

7. **Results**: These overviews suggest significant advantages to using Gn-RHa versus CC/hMG/FSH ovulation induction protocols in IVF and

GIFT. The cycle cancellation rate was approximately three times lower with Gn-RHa, largely because of the abolition of spontaneous LH surges (common odds ratio 0.32, 95% CI 0.24-0.43). A significant improvement was noted in the clinical pregnancy rate following both IVF (common odds ratio 1.86, 95% CI 1.33-2.44) and GIFT (common odds ratio 2.23, 95% CI 1.24-4.51). When comparing short "flare-up" and longer "suppression" regimes, no significant difference was noted in the pregnancy rate (common odds ratio 0.92, 95% CI 0.59-1.43). There was no significant difference in the spontaneous abortion rate following Gn-RHa versus traditional protocols.

Five trials reported multiple pregnancy as an outcome (Neveu et al. 1987; Antoine et al. 1990; Ferrier et al. 1990; van de-Helder et al. 1990; Ron-El et al. 1991). The common odds ratio for this outcome was 2.56 (95% CI 0.95-6.91). Three trials reported data on moderate to severe OHSS (Antoine et al. 1990; van de-Helder et al. 1990; Ron-El et al. 1991). In two trials, no OHSS occurred following routine ovulation induction, but 3 (Antoine et al. 1990) and 10 cases were reported following Gn-RHa protocols. A fourth trial reported "excessive ovarian stimulation" as a reason for cycle cancellation, with seven cases following a short flare-up Gn-RHa protocol and one following a suppression protocol.

8. **Consistency of results across trials**: Studies were clinically heterogeneous in terms of population and intervention. Inclusion criteria ranged from ovulatory women less than 38 years of age with tubal factor infertility alone (Antoine et al. 1990) to all IVF patients with no age limit (Maroulis et al. 1991). Various types and protocols of Gn-RHa administration were used. These have been grouped in the comparisons of short flare-up versus long suppression regimes and Gn-RHa versus traditional ovulation induction. Despite these differences, data on clinical pregnancy following IVF and GIFT show no statistically significant heterogeneity. This may, however, be a function of the limited statistical power of the Breslow-Day test. Data on cycle cancellation and spontaneous abortion were heterogeneous. Differences in populations probably account for this.

9. **Risks and costs**: The possible increased risks of multiple pregnancy and ovarian hyperstimulation have been discussed in the results section. Gn-RHa use may be associated with hot flashes for 2-3 d at the start of treatment. The additional direct cost per treatment cycle (leuprolide 0.1 mg for 14 d) is approximately $170.00. If used in a suppressive regime, additional hMG may also be required. These costs are balanced by the reduced rate of cycle cancellation and the potential for increased efficiency through improved clinical pregnancy rates.

10. **Implications for practice**: The routine use of Gn-RHa protocols in IVF and GIFT will significantly reduce cycle cancellation, improve the ongoing clinical pregnancy rate, and potentially provide more embryos for transfer in natural cycles following cryopreservation.

11. **Implications for research**: The efficacy of this approach, compared with more traditional OI protocols, is strongly supported by these data. However, the potential for publication bias must be remembered. Further trials of the cost-effectiveness and efficacy of different Gn-RHa protocols may be useful. Also, the possibility that multiple pregnancy and ovarian hyperstimulation may be increased following Gn-RHa use needs to be evaluated further. Lastly, as with all trials in IVF, the outcome of live birth should be considered and, when possible, reported.

12. **Conclusions**: A policy of routine Gn-RHa ovulation induction in IVF and GIFT can be expected to reduce cycle cancellation, improve ongoing clinical pregnancy rates, and provide more embryos for transfer in natural cycles following cryopreservation. Clinicians should be aware that the risk of OHSS and multiple pregnancy may be increased with this approach.

Table 12.1 Controlled Trials Comparing Gn-RHa with Other Ovulation Induction Protocols for IVF and GIFT

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Polson 1991 3/3/2/2	Centralized randomization by telephone using random number list*	120 (120)	56 (56)	Tubal or idiopathic infertility Previous poor stimulation excluded IVF and GIFT patients	Buserelin 600 or 1 200 µg IN daily Suppression	hMG alone	Clinical pregnancy Spontaneous abortion*	One or two treatment cycles	
Antoine 1990 2/3/2/2	Randomized using sealed envelopes*	90 (90)	90 (90)	Ovulatory < 38 years of age Tubal infertility No male factor IVF patients	Decapeptyl 3.75 mg depot intramuscular (IM) Suppression	hMG alone	Clinical pregnancy Spontaneous abortion Multiple pregnancy OHSS	One cycle*	

Table 12.1 (*cont'd*)

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Maroulis 1991 1/3/3/2	Quasi-random, alternating patients	99 (99)	93 (93)	IVF patients, all indications No age limit	Leuprolide 0.75-1 mg daily SC Flare-up or suppression	hMG/FSH	Implantation Clinical pregnancy Spontaneous abortion*	One cycle*	Randomization schedule changed during trial
van de-Helder 1990 1/3/3/2	Randomized, method not described	101 (101)	52 (52)	< 41 years of age Tubal infertility First cycle Male factor excluded IVF patients	Buserelin IN 600 µg Flare-up or suppression	hMG alone	Clinical pregnancy Spontaneous abortion Multiple pregnancy OHSS	One cycle	
Abdalla 1990 1/3/2/2	Quasi-random, alternating days	118 (118)	102 (102)	IVF and GIFT patients	Buserelin IN 100 µg for 5 d Flare-up	CC 100 mg days 2-6 + hMG	Clinical pregnancy Spontaneous abortion Live birth	1-3 cycles	Combined GIFT/IVF data reported Two-thirds of GIFT patients received Gn-RHa
Neveu 1987 1/3/2/2	Randomized, method not described	10 (10)	10 (10)	Tubal factor 28-38 years of age All had previously successful	Buserelin 0.3 mL SC Suppression	FSH alone	Clinical pregnancy Spontaneous abortion Multiple pregnancy	One cycle	

1991 1/3/2/2	method not described	(151)	(151)	with no exclusions	3.2 mg IM depot Suppression	alone	rate Clinical pregnancy Multiple pregnancy Live birth OHSS	cycles	out of 276 patients Approximately 50 patients had a single cycle
Kubik 1990 1/1/3/2	Quasi-random, alternating patients	? (60)	? (54)	First cycle IVF and GIFT patients	Leuprolide 50-100 mg SC Suppression	CC 100 mg days 5-9 + hMG	Clinical pregnancy Spontaneous abortion	One cycle	
Gonen 1991 1/1/2/2	Quasi-random, alternating patients	? (127)	? (59)	IVF patients reaching retrieval	Decapeptyl 3.2 mg IM suppression or buserelin 1 200-600 µg IN suppression	hMG alone	Clinical pregnancy Spontaneous abortion	1-2 month cycles	More patients with tubal factor in decapeptyl group
Ferrier 1990 1/1/2/1	Randomized, method not described	? (38)	? (55)	< 45 years of age IVF and GIFT patients	Leuprolide 0.1 mg SC daily Flare-up	CC 100 mg days 3-5 + hMG	Clinical pregnancy Spontaneous abortion Multiple pregnancy	1- 2 cycles	Major asymmetry between groups regarding diagnosis Different luteal support also

* Information obtained from author.

Figure 12.1 Controlled Trials Comparing Gn-RHa with Other Ovulation Induction Protocols in Patients Undergoing IVF and GIFT: Odds Ratios for Cycle Cancellation

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Polson	1991	7	120	15	56	0.17	0.06	0.48	0.0003
2/3/2/2	Antoine	1990	13	90	26	90	0.41	0.18	0.93	0.03
1/3/3/2	Maroulis	1991	12	99	30	93	0.29	0.12	0.64	0.001
1/3/3/2	van de-Helder	1990	14	101	9	52	0.77	0.28	2.11	0.74
1/3/2/2	Abdalla	1990	10	118	15	102	0.54	0.21	1.34	0.22
1/3/2/2	Neveu	1987	0	10	2	10	0.17	0	11.1	0.47
1/3/2/2	Ron-El	1991	5	151	41	151	0.09	0.03	0.25	0.000
1/1/3/2	Kubik	1990	8	60	21	54	0.24	0.09	0.66	0.004
1/1/2/1	Ferrier	1990	9	38	14	55	0.91	0.31	2.63	0.96
Common odds ratio and 95% CI							0.32	0.24	0.43	0.0000

Breslow-Day = 20.4, p = 0.01

* p value based on M-H corrected chi-square

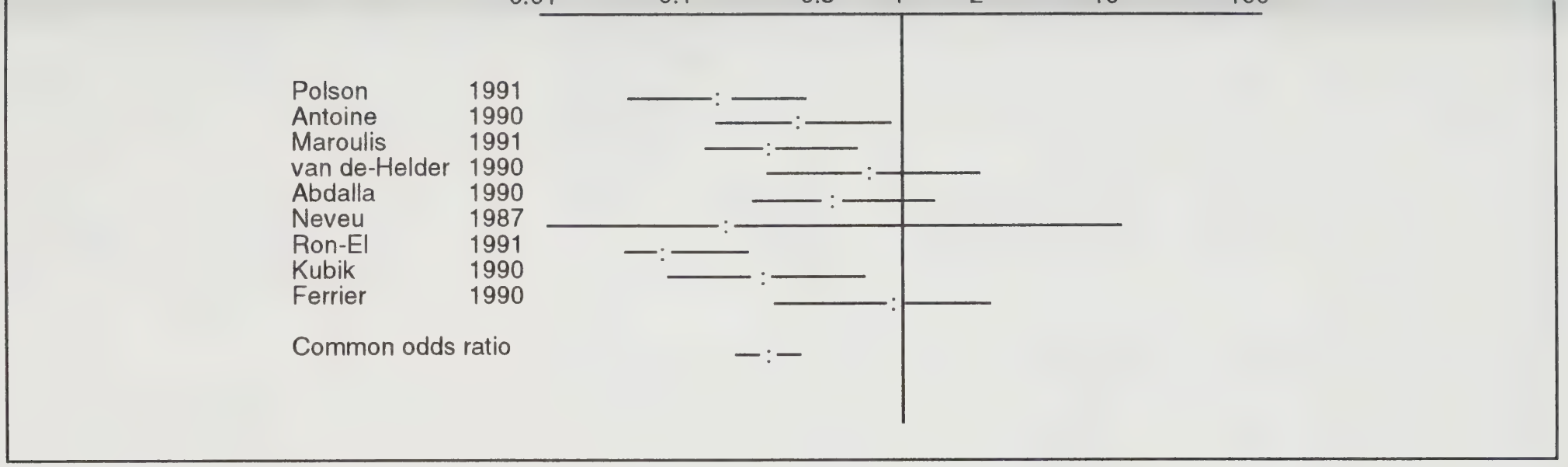

Polson 1991
Antoine 1990
Maroulis 1991
van de-Helder 1990
Abdalla 1990
Neveu 1987
Ron-El 1991
Kubik 1990
Ferrier 1990
Common odds ratio

Table 12.2 Controlled Trials Comparing Gn-RHa Flare-up with Gn-RHa Suppression Regimes for Ovulation Induction in IVF and GIFT

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Flare-up method	Suppression method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Flare-up**	**Suppression**						
Maroulis 1991 1/3/3/2	Quasi-random, alternating patients	? (35)	? (64)	All patients with indications for IVF	Leuprolide 0.75 mg SC daily	Leuprolide 1.0 mg SC daily	Clinical pregnancy	One cycle	Randomization schedule changed during trial
Remorgida 1989 1/3/3/2	Quasi-random, allocation by chart number*	82 (82)	96 (96)	First treatment cycle <40 years of age All patients with indications for GIFT	Buserelin 1 000 µg IN daily	Buserelin 1 000 µg IN daily	Clinical pregnancy Excessive ovarian response as a cause for cancellation	One cycle	
van de-Helder 1990 1/3/3/2	Randomized, method not described	51 (51)	50 (50)	<41 years of age Tubal infertility First cycle Male factor excluded GIFT patients	Buserelin 600 µg IN daily	Buserelin 600 µg/d IN	Clinical pregnancy Multiple pregnancy	One cycle	

1989 1/3/2/2	method not described	(9)	(9)	patients <40 years of age Tubal infertility Both ovaries present	900 µg IN daily	900 µg IN daily	response Clinical pregnancy	cycle
Dirnfeld 1991 1/3/1/2	Randomized using "table of random numbers"	26 (26)	28 (28)	One or two previous poor stimulation cycles IVF patients	Buserelin 600 µg/d, cycle day 1	Buserelin 1 000 µg/d 15-30 d pre-induction	Clinical pregnancy	One cycle

* Information obtained from author.

Figure 12.2 Controlled Trials Comparing Gn-RHa with Other Ovulation Induction Protocols in Patients Undergoing IVF: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
3/3/2/2	Polson	1991	11	92	3	46	1.95	0.47	9.33	0.49
2/3/2/2	Antoine	1990	19	90	11	90	1.92	0.80	4.66	0.16
1/3/3/2	Maroulis	1991	14	99	14	93	0.93	0.38	2.22	0.98
1/3/3/2	van de-Helder	1990	23	101	5	52	2.77	0.91	8.97	0.08
1/3/3/2	Abdalla[1]	1990	10	41	5	42	2.31	0.65	9.10	0.24
1/3/3/2	Neveu	1987	6	10	1	10	13.5	0.92	423.00	0.07
1/3/3/2	Ron-El	1991	39	151	19	151	2.42	1.27	4.62	0.006
1/1/3/2	Kubik	1990	7	34	2	26	2.67	0.56	24.10	0.311
1/1/2/2	Gonen[1]	1991	26	127	10	59	1.26	0.53	3.05	0.71
1/1/2/1	Ferrier[1]	1990	1	23	6	32	0.20	0.009	1.90	0.25
Common odds ratio and 95% CI							1.86	1.33	2.44	0.0002

Breslow-Day = 0.147, p = 0.701

* p value based on M-H corrected chi-square

[1] Data reported per retrieval only

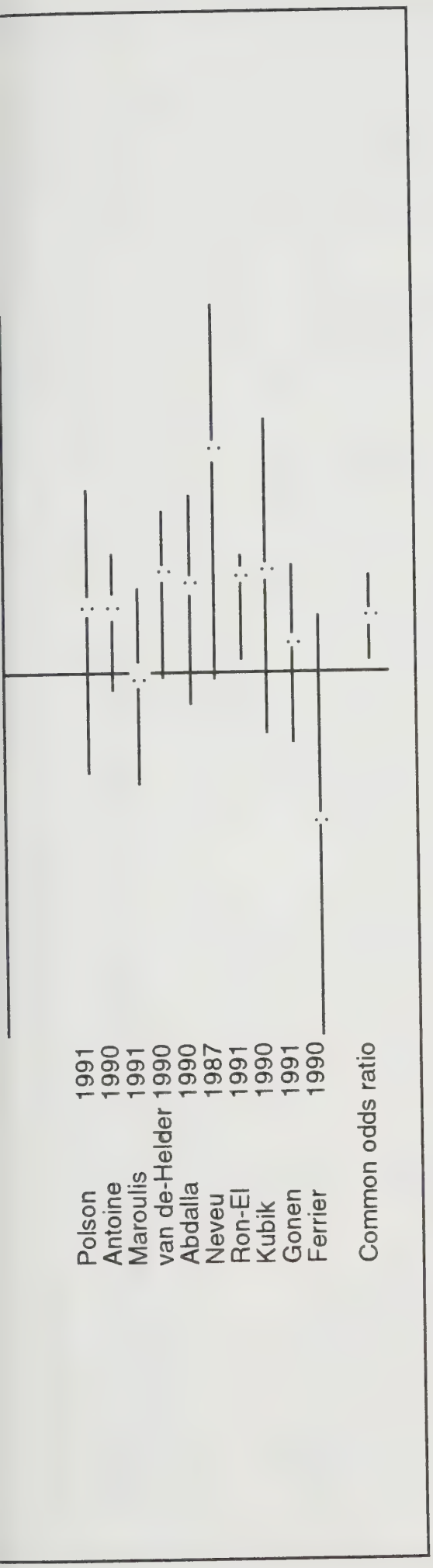

Polson 1991
Antoine 1990
Maroulis 1991
van de-Helder 1990
Abdalla 1990
Neveu 1987
Ron-El 1991
Kubik 1990
Gonen 1991
Ferrier 1990
Common odds ratio

Figure 12.3 Controlled Trials Comparing Gn-RHa with Other Ovulation Induction Protocols in Patients Undergoing GIFT: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Obser-vations	Total	Obser-vations	Total		Lo	Hi	
3/3/2/2	Polson	1991	9	24	0	10	12.9	0.88	999	0.07
1/3/2/2	Abdalla[1]	1990	23	64	9	36	1.68	0.62	4.63	0.37
1/1/3/2	Kubik	1990	16	26	11	28	2.47	0.83	6.90	0.18
1/1/2/1	Ferrier[1]	1990	2	6	2	9	1.75	0.10	31.1	0.91
Common odds ratio and 95% CI							2.23	1.24	4.51	0.01

Breslow-Day = 2.99, p = 0.39

* p value based on M-H corrected chi-square

[1] Data reported per retrieval only

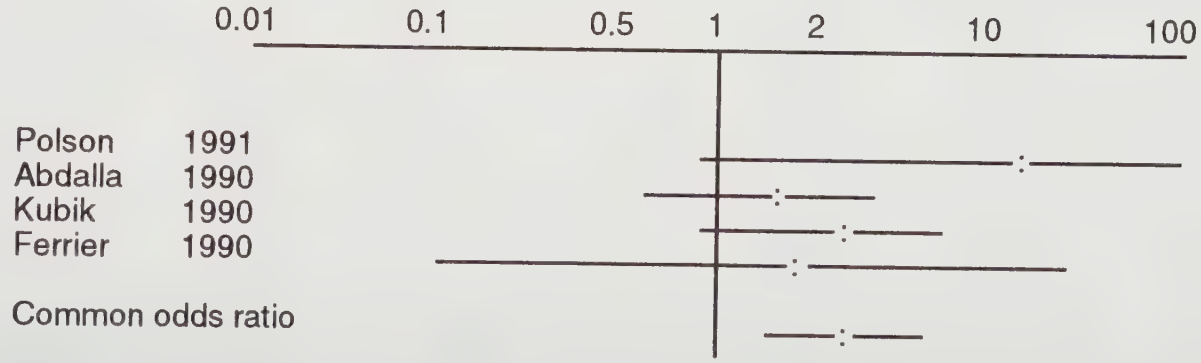


Figure 12.4 Controlled Trials Comparing GN-RHa "Flare-up" and "Suppression" Protocols in Patients Undergoing IVF and GIFT: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/3/3/2	Maroulis	1991	5	35	9	64	1.02	0.27	3.75	0.79
1/3/3/2	Remorgida	1989	25	82	31	96	0.92	0.46	1.82	0.92
1/3/3/2	van de-Helder	1990	14	51	9	50	1.72	0.60	4.95	0.27
1/3/2/2	Loumaye	1989	1	9	2	9	0.43	0.01	8.77	0.000
1/3/1/2	Dirnfeld	1991	2	26	8	28	0.20	0.03	1.20	0.11
Common odds ratio and 95% CI							0.92	0.59	1.43	0.79

Breslow-Day = 5.51, p = 0.24

* p value based on M-H corrected chi-square

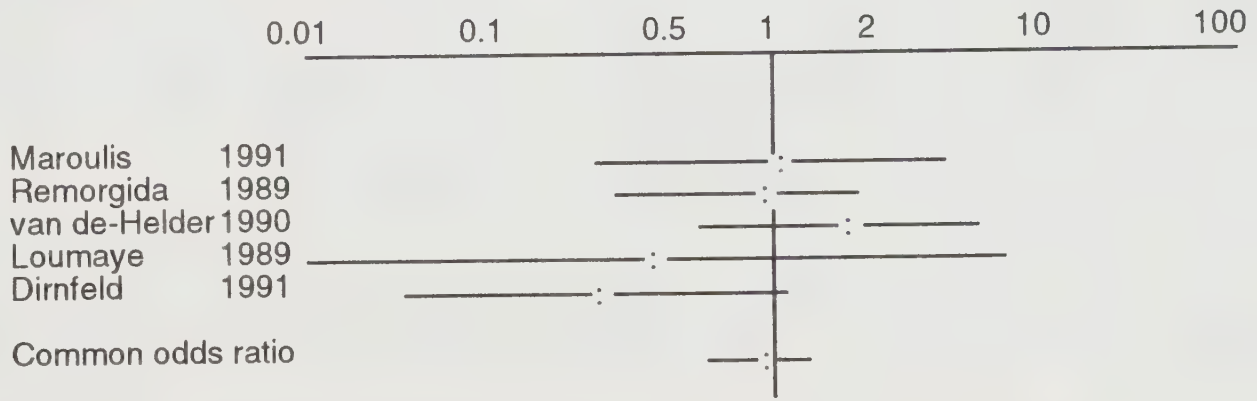


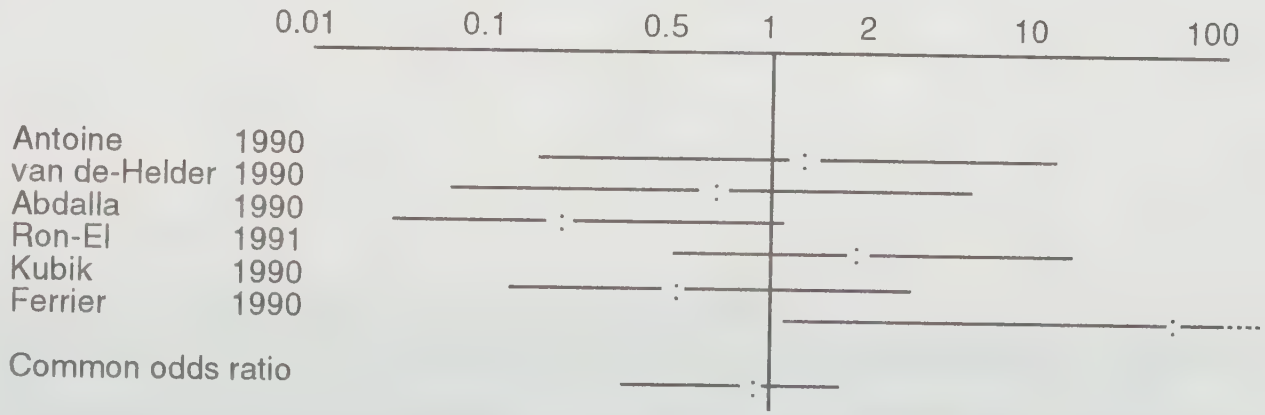
Figure 12.5 Controlled Trials Comparing GN-RHa with Other Ovulation Induction Protocols in Patients Undergoing IVF or GIFT: Odds Ratios for Spontaneous Abortion

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Obser-vations	Total	Obser-vations	Total		Lo	Hi	
2/3/2/2	Antoine	1990	4	19	2	11	1.20	0.14	11.9	0.78
1/3/3/2	van de-Helder	1990	7	23	2	5	0.66	0.06	7.34	0.012
1/3/2/2	Abdalla	1990	3	33	5	14	0.18	0.26	1.12	0.07
1/3/2/2	Ron-El	1991	7	39	2	19	1.86	0.30	14.7	0.73
1/1/3/2	Kubik	1990	6	23	5	13	0.57	0.10	3.02	0.69
1/1/2/1	Ferrier	1990	2	2	0	8	85	1.28	999	0.04
Common odds ratio and 95% CI							0.85	0.43	1.68	0.33

Breslow-Day = 16.5, p = 0.006

* p value based on M-H corrected chi-square



Overview Number: 13 (Table 13, Figures 13.1 and 13.2)

Title: **Progesterone Luteal Phase Support Versus no Treatment or Placebo in Women Undergoing IVF and GIFT**

Editor: E.G. Hughes

Parts of this overview:

1. Clinical pregnancy (seven trials)
2. Ongoing pregnancy (four trials)

Editorial Commentary

1. **Objective:** To evaluate the efficacy of progesterone administration during the luteal phase of women undergoing IVF or GIFT.
2. **Inclusion criteria for trials in this overview:** Randomized or quasi-randomized trials comparing progesterone administered vaginally, rectally, or intramuscularly (IM) versus placebo or no treatment.
3. **Trials excluded:** Van Steirteghem et al. (1988) — data from IVF and GIFT patients were not reported separately, allowing for significant bias if one group included more GIFT patients than the other; Chang et al. (1989) — two progesterone protocols compared.
4. **Trials included**: Belaisch-Allart et al. (1987); Kupferminc et al. (1990); McBain et al. (1987); Trounson et al. (1986); Yovich et al. (1985, 1991); Leeton et al. (1985).
5. **Unpublished data:** None identified.
6. **Methodological quality:** Four of seven studies included were quasi-randomized with sequential allocation (Leeton et al. 1985; Yovich et al. 1985, 1991; McBain et al. 1987), and one was published only in abstract form (McBain et al. 1987). There remains concern in these studies over the completeness of follow-up because treatment allocation was apparently undertaken at the outset of each cycle, but inclusion in the analysis was based on embryo transfer.
7. **Results**: The combined odds ratio for clinical pregnancy following progesterone luteal support was 1.22 (95% CI 0.94-1.57). Thus, if a positive effect exists, it is small. The combined odds ratio for ongoing pregnancy (clinical pregnancy minus spontaneous abortion) following treatment was 1.56 (95% CI 0.92-2.64). However, the unusually high spontaneous abortion rate (57%) in the no-treatment group of one study (Yovich et al. 1991) accounts for much of this effect. A sensitivity analysis excluding these data gives a revised common odds ratio of 1.30 (95% CI 0.71-2.40, $p = 0.49$).
8. **Consistency of results across trials:** The populations studied are similar: six out of seven trials reporting clinical pregnancy in

consecutive IVF or GIFT cycles. The treatments used were oral dydrogesterone in two studies, IM progesterone in four studies, and vaginal progesterone in one study. Despite these differences, there is no statistically significant heterogeneity with regard to data describing clinical and ongoing pregnancy.

9. **Risks and costs:** Luteal phase progesterone use is associated with no major maternal side-effects. Available data do not suggest any increased risk of fetal anomaly. The direct cost of treatment (50 mg BID for 14 d) is approximately $21.00.

10. **Implications for practice:** The routine use of luteal phase support with progesterone in patients undergoing IVF or GIFT following CC/hMG/FSH ovulation induction is not supported by these data.

11. **Implications for research:** As the total sample size of combined studies is 705 (treatment) versus 699 (control), further studies of larger sample sizes may be useful in answering this question. Patients receiving ovulation induction protocols that include Gn-RHa are particularly worthy of study because they may be susceptible to corpus luteum dysfunction (see overview 14).

12. **Conclusions:** Routine luteal phase support following ovulation induction, with and without Gn-RHa, requires further study. The data available demonstrate no significant benefit when progesterone is given following non-Gn-RHa-based ovulation induction protocols.

Table 13. Randomized Controlled Trials Comparing Progesterone with Placebo or No Treatment in Women Undergoing IVF or GIFT Following Ovulation Induction with CC/hMG/FSH

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Notes
Validity score		**Experimental**	**Control**					
Belaisch-Allart 1987	Double-blind, randomization, method not described	141 (141)	145 (145)	286 consecutive IVF cycles	Dydrogesterone 10 mg TID big mouth (PO)	Placebo TID	Clinical pregnancy	Randomized on day of retrieval
3/3/1/2								
Kupferminc 1990	Random allocation, method not described	54 (54)	51 (51)	Consecutive IVF patients No exclusions	Dydrogesterone 10 mg TID PO	Placebo PO TID	Chemical and clinical abortion Clinical pregnancy	Placebo versus dydrogesterone "blinded"
1/3/1/2								
McBain 1987	Quasi-random, sequential allocation	172 IVF (172)	173 (173)	Consecutive IVF and GIFT patients	Progesterone pessaries 50 mg daily for 14 d	No treatment	Clinical pregnancy	Abstract only Author information is being sought
1/3/1/2		125 GIFT (125)	125 (125)					

Table 13. (*cont'd*)

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Notes
Validity score		**Experimental**	**Control**					
Trounson 1986 1/3/1/2	Random allocation, method not described	14 (14)	14 (14)	Consecutive IVF patients	Progesterone in oil 25 mg IM 50 mg IM within 36 h of ovulatory hCG	No treatment	Clinical pregnancy Spontaneous abortion	Minimal exposure to luteal progesterone Two doses only within 36 h of ovulatory hCG injection
Yovich 1985 1/1/1/2	Quasi-random, sequential allocation	? (77)	? (60)	IVF patients undergoing 1st or 2nd cycle	Progesterone in oil 50 mg IM days 0,1,2,3,4 post-retrieval	No treatment	Serum progesterone Clinical pregnancy	Allocation at treatment cycle outset Inclusion based on embryo transfer
Yovich 1991 1/1/1/2	Quasi-random, sequential allocation	? (50)	? (51)	GIFT patients age < 39 years > 3 years infertility Ovulatory No male factor Unexplained or mild	Progesterone in oil 50 mg IM days 0,1,2,3,4 post-retrieval	No treatment	Implantation Clinical pregnancy Abortion	Part of a four-arm trial comparing no treatment with IM progesterone, IM hCG, or a combination of hCG +

1985 1/1/1/2	sequential allocation	(72)	(80)	IVF patients	oil 50 mg IM daily days 7-16 post-retrieval	treatment	Spontaneous abortion	allocation, treatment and control groups asymmetrical, suggesting incomplete follow-up

Figure 13.1 Randomized Controlled Trials Comparing Progesterone Luteal Phase Support with Placebo or No Treatment in Women Undergoing IVF or GIFT: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Obser-vations	Total	Obser-vations	Total		Lo	Hi	
3/3/1/2	Belaisch-Allart	1987	27	141	20	145	1.48	0.75	2.91	0.29
1/3/1/2	Kupferminc	1990	16	54	14	51	1.11	0.44	2.83	0.97
1/3/1/2	McBain	1987	74	297	70	298	1.08	0.73	1.60	0.76
1/3/1/2	Trounson	1986	4	14	4	14	1.00	0.15	6.85	0.68
1/1/1/2	Yovich	1985	11	77	5	60	1.83	0.54	6.49	0.42
1/1/1/2	Yovich	1991	16	50	14	51	1.24	0.48	2.19	0.78
1/1/1/2	Leeton	1985	14	72	12	80	1.36	0.54	3.46	0.16
Common odds ratio and 95% CI							1.22	0.94	1.57	0.01

Breslow-Day = 1.45, p = 0.96

* p value based on M-H corrected chi-square

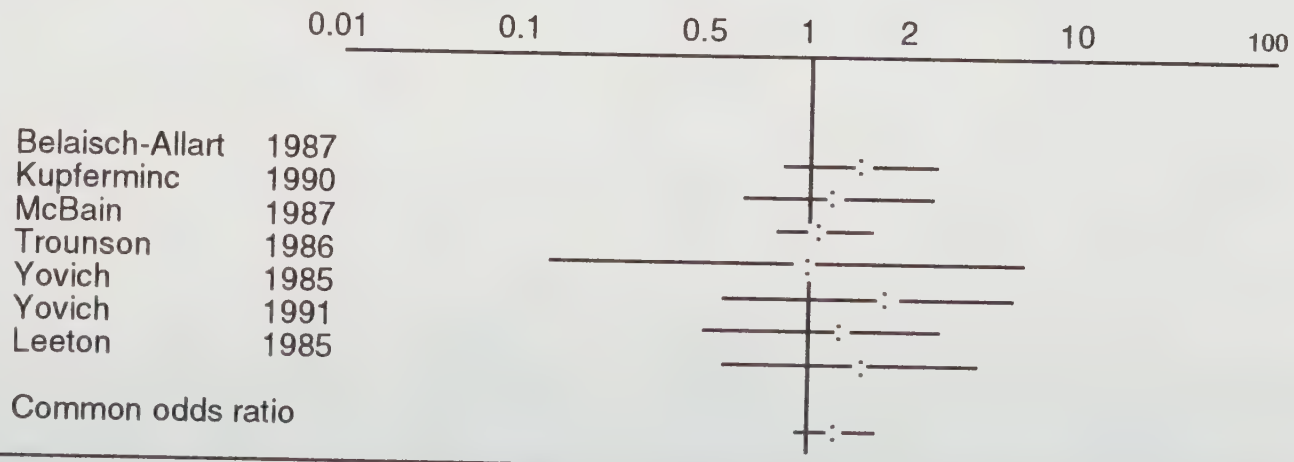


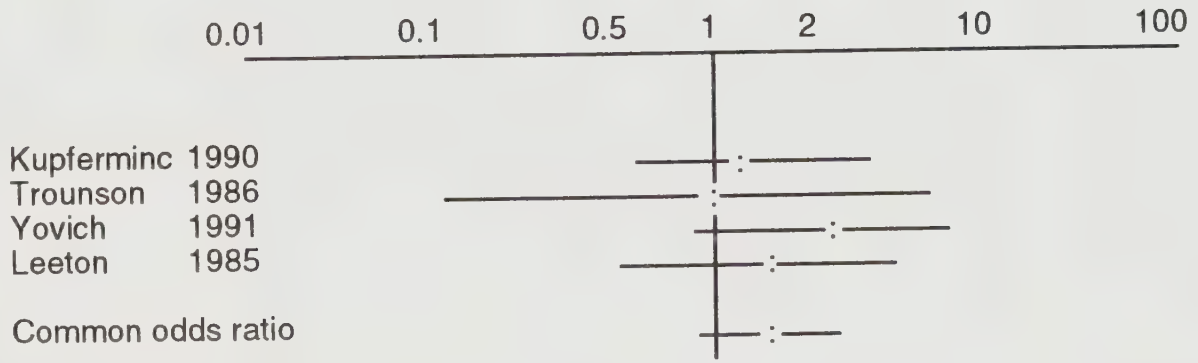
Figure 13.2 Controlled Trials Comparing Progesterone Luteal Phase Support with Placebo or No Treatment in Women Undergoing IVF or GIFT: Odds Ratios for Ongoing Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/3/1/2	Kupferminc	1990	13	54	11	51	1.15	0.42	3.16	0.94
1/3/1/2	Trounson	1986	3	14	3	14	1.00	0.11	8.36	0.65
1/1/1/2	Yovich	1991	13	50	6	51	2.63	0.82	8.72	0.12
1/1/1/2	Leeton	1985	12	72	9	80	1.58	0.57	4.40	0.53
Common odds ratio and 95% CI							1.56	0.92	2.64	0.12

Breslow-Day = 1.61, p = 0.66

* p value based on M-H corrected chi-square



Overview number: 14 (Tables 14.1 and 14.2, Figures 14.1 and 14.4)

Title: **Controlled Trials Comparing hCG with Placebo or No Treatment in Women Undergoing IVF or GIFT**

Editor: E.G. Hughes

Parts of this overview:

1. Clinical pregnancy following CC/hMG/FSH (five trials)
2. Ongoing pregnancy following CC/hMG/FSH (four trials)
3. Clinical pregnancy following Gn-RHa/hMG/FSH (three trials)
4. Ongoing pregnancy following Gn-RHa/hMG/FSH (three trials)

Editorial Commentary

1. **Objective**: To evaluate the efficacy of hCG luteal support following IVF or GIFT compared with placebo or no treatment.
2. **Inclusion criteria for trials in this overview:** Randomized and quasi-randomized trials comparing hCG administered intramuscularly compared with placebo, progesterone, or no treatment. Trials comparing hCG with progesterone were included on the basis of overview 13.
3. **Trials excluded:** Smitz et al. (1988) — IVF and GIFT data not reported separately.
4. **Trials included:** Kupferminc et al. (1990); Herman et al. (1990); Trounson et al. (1986); Yovich et al. (1991); Buvat et al. (1988, 1990); Nader et al. (1988); Smith et al. (1989).
5. **Unpublished data:** None identified.
6. **Methodological quality:** Five of eight trials were quasi-randomized. In two, follow-up post-randomization was incomplete (Buvat et al. 1988; Yovich et al. 1991). None was blinded. Two of the trials were multi-armed and included progesterone (Kupferminc et al. 1990; Yovich et al. 1991). Two others compared hCG with progesterone alone (Nader et al. 1988; Buvat et al. 1990).
7. **Results:** No significant difference was observed between hCG and placebo or no treatment after CC/hMG/FSH. The common odds ratio for clinical pregnancies was 1.17 (95% CI 0.69-1.90). When considering ongoing pregnancy, the common odds ratio was 1.58 (95% CI 0.85-2.96). Data from the three trials examining hCG support following ovulation induction with Gn-RHa, however, show a significant treatment effect. The common odds ratio for clinical pregnancy was 3.47 (95% CI 1.91-6.12) and for ongoing pregnancy was 4.63 (95% CI 2.45-8.10) in this group of studies.

8. **Consistency of results across trials:** There was no statistically significant heterogeneity demonstrated. However, it should be noted that two trials that used progesterone in control patients have been included (Nader et al. 1988; Buvat et al. 1990). Otherwise, the populations and interventions were clinically homogeneous.

9. **Risks and costs:** Although few data are available, the use of hCG luteal phase support may increase the risk of moderate to severe ovarian hyperstimulation. Two cases of moderate OHSS were observed following hCG and none following progesterone in one study (Buvat et al. 1990). Five cases of moderate to severe OHSS were reported following Gn-RHa versus none in the no-treatment group of a second trial (Herman et al. 1990). The direct cost per treatment cycle (hCG 2 500 IU × three doses) is $48.85.

10. **Implications for practice:** These data do not support the routine use of hCG in IVF or GIFT following ovulation induction with CC/hMG/FSH. However, there is evidence of significant benefit following Gn-RHa ovulation induction protocols.

11. **Implications for research:** These findings are derived from a small sample size, providing inadequate power to demonstrate small but clinically important differences between treatment and control groups. Therefore, additional trials are warranted to address the question of hCG use following CC/hMG/FSH ovulation induction. Although hCG luteal support appears to enhance significantly the clinical pregnancy rate following ovulation induction with Gn-RHa, additional studies are also warranted to assess the questions of efficacy and risk, particularly with respect to OHSS.

12. **Conclusions:** The routine use of hCG luteal phase support following CC/hMG/FSH protocols is unproven. Following Gn-RHa ovulation induction, hCG luteal support is recommended, although more studies are needed to further assess the efficacy and side-effects of this approach.

Table 14.1 Randomized Controlled Trials Comparing hCG with Placebo, Progesterone, or No Treatment in Women Undergoing IVF or GIFT Following Ovulation Induction with CC/hMG/FSH

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Nader 1988 1/3/2/1	Random method not described	10 (10)	10 (10)	Consecutive IVF patients	hCG 1 500 IU days 4,7,10,13, post-retrieval	Progesterone 25 µg in oil days 4-18 post-transfer	Endocrine response Clinical pregnancy Ongoing pregnancy	One cycle	Small sample size CC/hMG or hMG alone, both used in ovulation induction
Kupferminc 1990 1/3/1/2	Random, method not described	51 (51)	51 (51)	Consecutive IVF patients No exclusions	hCG 2 500 IU days 3,6,10 following embryo transfer	Placebo PO TID	Chemical and clinical abortion Clinical pregnancy	One cycle	Part of a three-arm trial including oral progesterone
Trounson 1986 1/3/1/2	Random, method not described	14 (14)	14 (14)	Consecutive IVF patients	hCG 5 000 IU IM 24 h post-initial hCG	No treatment	Clinical pregnancy Spontaneous abortion	One cycle	Minimal exposure to luteal hCG Only one injection 24 h post-initial ovulatory

Yovich 1991 1/1/1/2	Quasi-random, alternating by patient	(55)	(51)	age > 3 years infertility Unexplained or mild endometriosis No male factor Normal ovulation	IU IM days 4,7,10,13 post-retrieval		Clinical pregnancy Abortion		four-arm trial comparing no treatment with IM progesterone, IM hCG, or a combination of hCG and progesterone
Buvat 1988 1/1/1/1	Quasi-random, alternating by date	? (60)	? (56)	Consecutive IVF patients reaching oocyte retrieval	hCG 1 500 IU IM days 2,4,6 post-transfer	No treatment	Clinical pregnancy Implantation rate OHSS	One cycle	Spontaneous abortion rate was not reported

Figure 14.1 Controlled Trials Comparing hCG Luteal Phase Support with Placebo or No Treatment: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

Validity score	1st author	Year	Experimental		Control		Odds ratio	95% CI		p*
			Obser-vations	Total	Obser-vations	Total		Lo	Hi	
1/3/2/1	Nader	1988	3	10	0	10	9.8	0.45	999	0.22
1/3/1/2	Kupferminc	1990	12	51	14	51	0.82	0.30	2.17	0.82
1/3/1/2	Trounson	1986	4	14	4	14	1.00	0.14	0.85	0.68
1/1/1/2	Yovich	1991	19	55	14	56	1.39	0.56	3.47	0.56
1/1/1/1	Buvat	1988	9	60	8	56	1.06	0.34	7.32	0.88
Common odds ratio and 95% CI							1.17	0.69	1.90	0.88

Breslow-Day = 3.97, p = 0.41

* p value based on M-H corrected chi-square

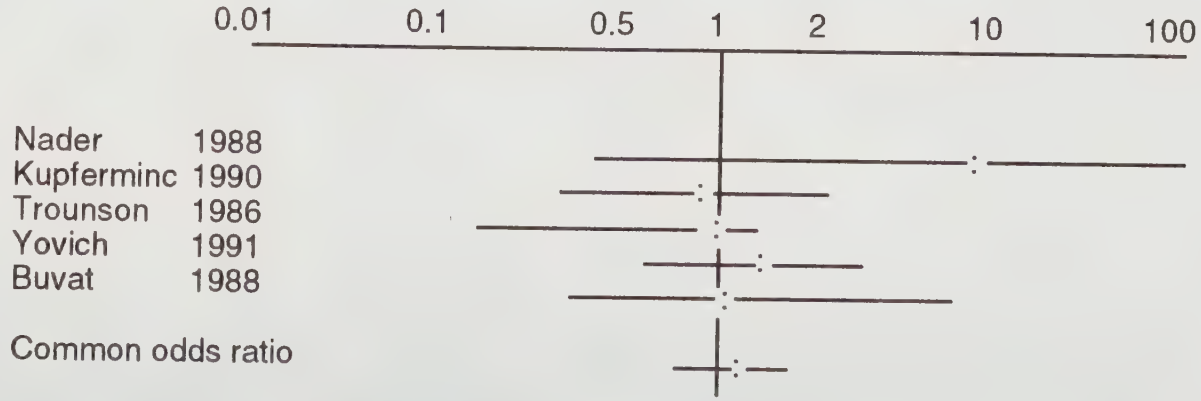


Table 14.2 Controlled Trials Comparing hCG Luteal Support with No Treatment or Progesterone in IVF Following Ovulation Induction with Gn-RHa Protocols

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Herman 1990 1/3/1/2	Quasi-random, alternating by patient	18 (18)	19 (18)	Consecutive IVF patients	hCG 2 500 IU IM days 0,2,5,8 post-transfer	No treatment	Clinical pregnancy OHSS	One cycle	Ovulation induction with Gn-RHa suppression/ hMG
Smith 1989 1/3/1/2	Quasi-random, by day of hCG ovulatory dose	61 (61)	54 (54)	Consecutive IVF patients with more than one embryo transferred	hCG 2 500 IU IM days 3 and 6 post-ovulation	No luteal support	Serum estradiol and progesterone (E_2P) Implantation Clinical pregnancy Spontaneous abortion Multiple pregnancy	One cycle	Asymmetry in size between treatment and control group

Table 14.2 (*cont'd*)

1st author year	Method of allocation	Cycles allocated (nos. included in analysis)		Entry criteria	Experimental method	Control method	Main outcomes measured	Duration of follow-up	Notes
Validity score		**Experimental**	**Control**						
Buvat 1990 1/1/1/2	Quasi-random, by day of retrieval	? (70)	? (70)	Consecutive IVF patients reaching retrieval	hCG 1 500 IU IM days 0,2,3,4 post-transfer	Micronized progesterone 400 µg PO daily-1-menses*	Serum E_2P Implantation Clinical pregnancy Spontaneous abortion	One cycle	Randomized on day of retrieval Analyzed by embryo transfer Loss to follow-up of failed fertilization patients

* Medication was begun the day after retrieval i.e., one day before embryo transfer.

Figure 14.2 Controlled Trials Comparing hCG Luteal Support with Placebo, Progesterone, or No Treatment in Women Undergoing IVF or GIFT: Odds Ratios for Ongoing Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/3/2/1	Nader	1988	3	10	0	10	9.8	0.45	999	0.22
1/3/1/2	Kupferminc	1990	10	51	11	51	0.89	0.31	2.56	1.0
1/3/1/2	Trounson	1986	3	14	3	14	1.00	0.12	8.45	0.65
1/1/1/2	Yovich	1991	14	55	6	51	2.56	0.82	8.33	0.12
Common odds ratio and 95% CI							1.58	0.85	2.96	0.20

Breslow-Day = 4.86, p = 0.182

* p value based on M-H corrected chi-square

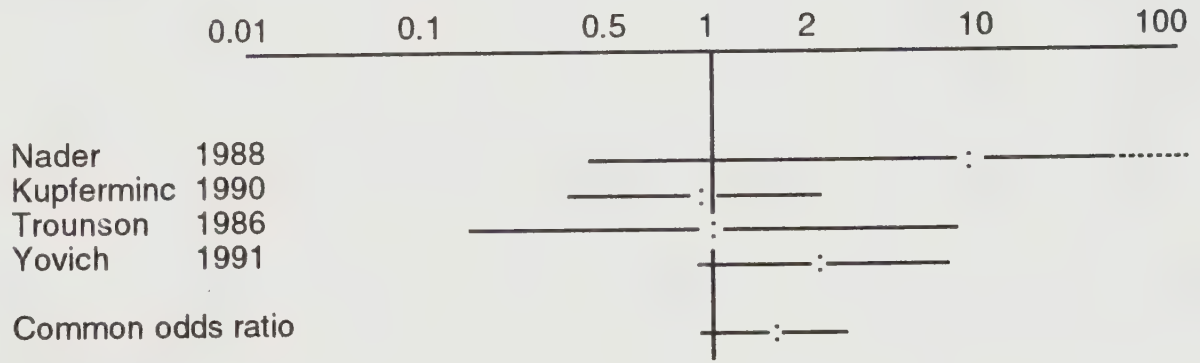


Figure 14.3 Controlled Trials Comparing hCG with Progesterone or No Treatment in Women Undergoing IVF Following Ovulation Induction with Gn-RHa: Odds Ratios for Clinical Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/3/1/2	Herman	1990	9	18	3	18	5.00	0.87	31.9	0.08
1/3/1/2	Smith	1989	25	61	8	54	3.99	1.49	11.0	0.004
1/1/1/2	Buvat	1990	22	70	10	70	2.75	1.10	6.94	0.027
Common odds ratio and 95% CI							3.47	1.91	6.12	0.0001

Breslow-Day = 0.6, p = 0.963

* p value based on M-H corrected chi-square

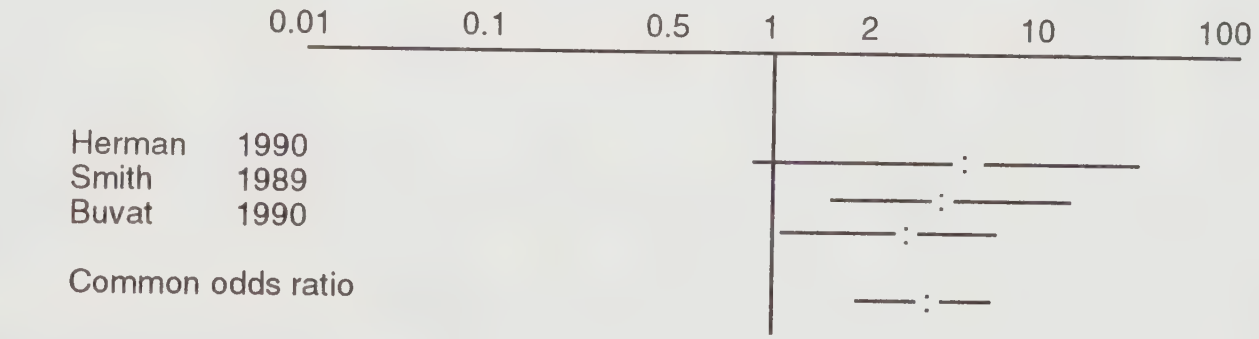


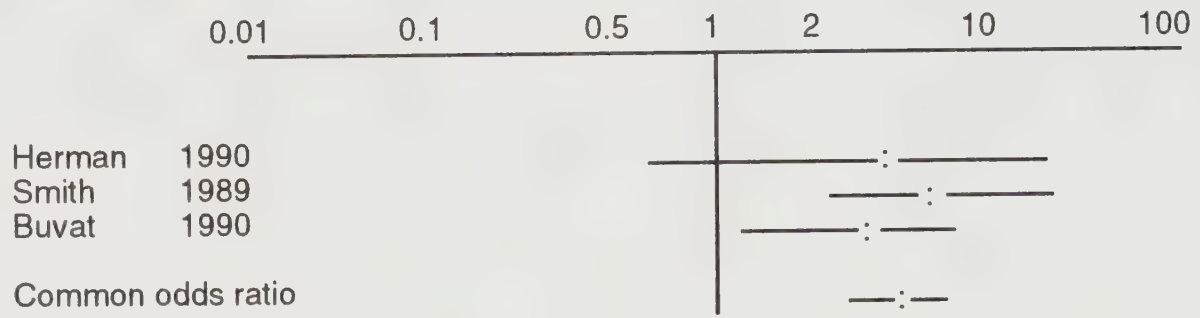
Figure 14.4 Controlled Trials Comparing hCG with Placebo, Progesterone, or No Treatment in Women Undergoing IVF after Gn-RHa Ovulation Induction: Odds Ratios for Ongoing Pregnancy

Method: Odds Ratio (Mantel-Haenszel)

			Experimental		Control			95% CI		
Validity score	1st author	Year	Obser-vations	Total	Obser-vations	Total	Odds ratio	Lo	Hi	p*
1/3/1/2	Herman	1990	9	18	3	18	4.0	0.69	25.5	0.15
1/3/1/2	Smith	1989	21	61	4	64	7.85	2.31	29.5	0.0002
1/1/1/2	Buvat	1990	21	70	8	70	3.32	1.25	9.0	0.013
Common odds ratio and 95% CI							4.63	2.45	8.10	0.0001

Breslow-Day = 1.41, p = 0.84

* p value based on M-H corrected chi-square



Summary and Conclusions

The most extensive data examining an individual treatment approach in assisted reproductive technology address the efficacy of Gn-RHa in IVF and GIFT. The routine use of Gn-RHa appears to increase the clinical pregnancy rate per treatment cycle by decreasing the rate of cancellation and possibly increasing the rate of embryo implantation. The costs of this treatment include the direct expense of the medication and, in suppressive regimes, the cost of additional gonadotropin. The possibility that these drugs result in increased rates of OHSS and multiple pregnancy deserves further study.

Luteal phase support with hCG appears to have a positive effect when used after Gn-RHa treatment. Again, the possibility of increased ovarian hyperstimulation needs to be assessed in further studies. The routine use of progesterone in the luteal phase is not supported by available evidence. Even the combined studies, however, have insufficient statistical power to rule out small but clinically significant therapeutic benefits.

Appendix 1. Structured Abstracts — Controlled Trials in Unexplained Infertility

Authors and Year: P.G. Crosignani, D.E. Walters, and A. Soliani (1991)

Title	"The ESHRE Multicentre Trial on the Treatment of Unexplained Infertility: A Preliminary Report."
Objective	To compare superovulation alone with a combination of superovulation and one of four other treatments — IUI, DIPI, GIFT, and IVF — in couples with unexplained infertility.
Design	Each of the 19 centres chose a pair of the five treatments noted above. Patients fulfilling inclusion criteria were then randomized to begin a cycle of treatment with one or the other of these approaches. If pregnancy did not occur during this first cycle, crossover to the alternate treatment was advised. The method of randomization was not reported.
Setting	Multicentre trial among 19 European infertility clinics.
Patients	Patients with unexplained infertility were admitted to the study if they fulfilled the following criteria: female age < 38 years; infertility duration > 36 months; women with at least one normal tube and ovary on laparoscopy; evidence of ovulation in two recent cycles based on plasma progesterone levels; semen analysis normal according to World Health Organization (WHO) criteria; patients had to refrain from sexual activity for

	6 d prior to and 3 d after treatment; and, finally, there must have been at least two months without treatment for infertility prior to study entry. Cervical and immunological criteria were not used because of the controversy surrounding the interpretation of these tests.
Interventions	These were not described in detail, but were applied as currently practised in each of the centres selecting them. The interventions were superovulation with hMG and a combination of superovulation with hMG and either IUI, DIPI, GIFT, or IVF.
Main Outcomes Measured	Chemical pregnancy; spontaneous abortion; clinical pregnancy. The reported analyses include spontaneous abortion and ongoing pregnancy.
Main Results	Using data from first cycles only, the mean cycle fecundity with superovulation alone was 17.4% compared with a range of 23.7-29.9% among the combination treatments. When data were combined with the second treatment cycle, the superovulation monthly fecundity was 15.2% compared with a range of 25.7-28.0% among the combination treatments. When both first- and second-cycle data were combined for the four combination treatments, the fecundity within this large group bordered on statistical significance ($p = 0.058$) when compared with a cycle fecundity rate for superovulation alone.
Conclusions	An estimate of approximately 2% was made for the spontaneous pregnancy rate in this patient group. All of the treatments, including superovulation alone, produced pregnancy rates that exceeded this spontaneous cycle fecundity. The confidence limits around these rates did not overlap 2%. These data suggest that all treatments were effective in enhancing conception during either one or two cycles of treatment. There was borderline statistical significance suggesting that superovulation alone was inferior to its use in combination with one of the four other treatment approaches. However, none of the treatments was clearly better than the others. It was interesting to note, however, that the less invasive treatments (IUI and DIPI) were as effective as GIFT and IVF.

Author and Year: D.C. Daly (1989)

Title	"Treatment Validation of Ultrasound-Defined Abnormal Follicular Dynamics as a Cause of Infertility."
Objective	To determine whether ovulation induction with CC or hMG improves conception in couples with unexplained infertility and in particular the subgroup of women showing abnormal follicular dynamics.
Design	Prospective cohort study.

Setting	Department of Obstetrics and Gynecology and Department of Radiology, University of Massachusetts Medical School, Worcester, Massachusetts.
Patients	Between March 1984 and February 1987, 109 patients with unexplained infertility were divided into three cohorts. The first showed evidence of abnormal follicular development on ultrasound as defined by rupture of small follicular size; luteinized unruptured follicle; follicular growth of < 1 mm/d for 3 d; or a plateau in growth for 2 d prior to rupture (n = 25). The second cohort was made up of patients who chose therapy with hMG ± IUI (n = 20). The final cohort was made up of those patients who elected to undergo no treatment (n = 47). Seventeen patients were lost to follow-up and were not included in the report.
Interventions	In the abnormal follicular development group, clomiphene was given for up to eight cycles in an indeterminate fashion and if unsuccessful it was followed by hMG. In the treatment group, patients received hMG and IUI in alternating cycles (55 cycles in 20 patients). There were also "no-treatment cycles" interspersed between these treatments, and data for spontaneous pregnancy during these cycles were reported separately. In the third cohort, patients were managed with no treatment.
Main Outcomes Measured	Monthly fecundity (viable pregnancy).
Main Results	The unexplained infertility patients electing no treatment were significantly younger than those with abnormal follicular development and those choosing treatment. Those undergoing no treatment had a monthly viable fecundity of 3.5% (95% CI 1.92-5.1). This varied little with age and duration of infertility. Those patients with abnormal follicular dynamics had a monthly viable fecundity of 25% (95% CI 14-36). Of the 20 patients who underwent hMG ± IUI, six conceived — the viable fecundity rate was 11% (95% CI 3-19). Two pregnancies occurred during 135 non-treatment cycles — viable fecundity rate 1.6% (95% CI not given). When monthly fecundity for control group B was calculated (treatment and non-treatment cycles over the mean of 17 months follow-up), it was 4.2%. This was not significantly different from the monthly fecundity for those patients not receiving treatment (3.5%).
Conclusions	Treatment with hMG and IUI appears to hasten the time to conception, but not the net pregnancy rate, in patients with no other evidence of follicular abnormality. As the cumulative pregnancy rate in the group with abnormal follicular development was significantly higher than that observed in

other patients, treatment with ovulation induction may be effective in this subgroup.

Authors and Year: J.L. Deaton et al. (1990)

Title	"A Randomized, Controlled Trial of Clomiphene Citrate and Intrauterine Insemination in Couples with Unexplained Infertility or Surgically Corrected Endometriosis."
Objective	To compare fecundity data in women with unexplained infertility or surgically treated endometriosis receiving clomiphene and timed IUI versus intercourse.
Design	Randomized crossover trial comparing clomiphene and IUI with intercourse. Four cycles of one approach were undertaken before crossing over.
Setting	University of Vermont College of Medicine, Burlington, Vermont.
Patients	All couples showed biphasic basal body temperature charts, a normal semen analysis, a normal post-coital test, a late luteal phase endometrial biopsy less than 2 d out of phase, and a normal hysterosalpingogram (HSG). Those found to have endometriosis on laparoscopy were treated with CO_2 laser and then admitted to the study. Tubal disease patients were excluded.
Interventions	During treatment cycles, women received clomiphene 50 mg on days 5-9. An ultrasound was done on the morning of day 12 during the first cycle, and this was moved to a more appropriate day during subsequent cycles. Based on the day 12 ultrasound, the projected day for the presence of an 18-mm follicle was determined and hCG was given on that day. Thirty-six hours after hCG, a semen sample for IUI was obtained. This was prepared using a swim-up procedure using Ham's F-10 medium. Patients were inseminated using a paediatric feeding tube. Control cycles involved intercourse around the time of ovulation. Basal body temperature charts were reviewed to "assure" that intercourse had occurred after an appropriate time.
Main Outcomes Measured	Pregnancy.
Main Results	Sixty-seven couples were enrolled. Ten couples (20 cycles) were subsequently excluded from the analysis because of either abnormal semen analysis or an anovulatory cycle. These cycles were apparently distributed evenly between the treatment groups. Another six couples were excluded before completion of the first cycle because of stress. A total of 51 couples were included in the analysis.

Of the 23 couples initially randomized to treatment, eight became pregnant and only 12 crossed over to the control group. One subsequently conceived during timed intercourse. Of the 28 couples initially randomized to the control group, four became pregnant and 23 crossed over. Six of the 23 subsequently conceived during clomiphene/IUI.

There were, therefore, a total of 14 conceptions during 148 treatment cycles (monthly fecundity 0.095). There were five conceptions during 150 control cycles (monthly fecundity 0.033). This represents a significant treatment effect ($\chi^2 = 4.71$, $p = 0.03$). There was a trend toward increased fecundity with secondary infertility, but female age, duration of infertility (non-significant), and unexplained versus treated endometriosis showed no significant effect.

Conclusions

The authors conclude that clomiphene and IUI in combination improve fecundity when compared with periovulatory intercourse in couples with either unexplained or surgically corrected endometriosis-related infertility.

Authors and Year: J. Evans et al. (1991)

Title

"A Comparison of Intrauterine Insemination, Intraperitoneal Insemination, and Natural Intercourse in Superovulated Women."

Objective

To compare, in women receiving ovarian hyperstimulation, IUI, DIPI, and natural intercourse.

Design

Randomized prospective crossover trial. Couples were randomly allocated initially to one of three treatment modalities. They then progressed to the next treatment if unsuccessful and received a total of four cycles of treatment within each group. Note: If a treatment was not possible because of technical problems, e.g., catheterization of the cervix for IUI, an alternative treatment was employed. Thus, there was crossover between and within treatment groups. Additional data were provided after the first part of this trial.

Setting

Department of Obstetrics and Gynaecology, University Hospital of Wales, Cardiff, United Kingdom.

Patients

Fifty-six couples were recruited, 22 with unexplained infertility. This was defined as follows: normal ovulation, with or without CC; normal semen analysis, $> 20 \times 10^6$/mL and > 50% motility; normal patent tubes; no cervical mucus problem; and a normal post-coital test. Patients also underwent anti-sperm antibody testing through a tray agglutination or sperm immobilization test. The mean duration of infertility was 6.1 years, and the mean female age in this study was 33.9 years. Patients with tubal disease or polycystic ovarian disease were excluded.

	There were also 22 patients with abnormal semen and 12 patients with anti-sperm antibodies within this trial.
Interventions	All patients received a combination of CC (100 mg for 5 d) and hMG (two ampoules on three separate days). IUI was performed 42 h after hCG. This followed a swim-up procedure. DIPI was timed in the same way, and natural intercourse was requested on day 13 of the cycle following an identical ovarian stimulation and assessment of response. All patients received 5 000 units of hCG in the luteal phase.
Main Outcomes Measured	Pregnancy.
Main Results	Pregnancy per treatment cycle in unexplained fertility with IUI was 1/26 (3.8%) and following IUI was 2/16 (12.5%). Following DIPI, 5/29 (17.2%) cycles were successful. Overall pregnancy rates in the semen and antibody groups were < 8% per cycle, except for 3/29 (10.3%) cycles following DIPI. It was mentioned that during the second part of the trial, randomization became "less strict."
Conclusions	The authors report a subgroup analysis comparing natural intercourse + IUI versus DIPI giving a p value of < 0.05, suggesting significant improvement with DIPI in unexplained infertility. The combined data from different patient groups again suggest a significance level of < 0.05 when comparing DIPI with other treatments. There were, however, significant methodological problems with this study, including the crossover design and the way in which patients randomized to one treatment might then have received another treatment.

Authors and Year: P. Fisch et al. (1989)

Title	"Unexplained Infertility: Evaluation of Treatment with Clomiphene Citrate and Human Chorionic Gonadotropin."
Objective	To determine whether CC or hCG increases the conception rate in couples with unexplained infertility.
Design	Double-blind, randomized controlled study comparing four treatment arms. This multicentre trial used central randomization, dispersing drugs through a pharmacy.
Setting	Five Canadian university hospitals.
Patients	The following criteria were necessary for entry into the study: primary infertility of two or more years' duration; proven ovulation with regular menstrual cycles and biphasic basal body temperature chart; serum progesterone > 10 µg/mL in the mid-luteal phase or an in-phase secretory endometrial biopsy in the late luteal phase; normal HSG; normal laparoscopy within the last two years; normal serum prolactin; and two normal semen analyses fulfilling WHO criteria.

Interventions	Four treatment groups were included: Group 1 — placebo tablets two PO on days 5-9 followed by placebo saline in IM injections on days 19, 22, 25, and 28 of the cycle. Group 2 — placebo tablets as above followed by hCG injections 5 000 IU given IM on days 19, 22, 25, and 28. Group 3 — clomiphene tablets 100 mg on days 5-9 followed by placebo saline injections in the luteal phase. Group 4 — clomiphene 100 mg on days 5-9 followed by hCG 5 000 IU on days 19, 22, 25, and 28 of the luteal phase. Treatment-independent pregnancies were recorded after randomization but before the onset of treatment, and for the six-month period following the trial. Pregnancy was defined as the visualization of a gestational sac with fetal heart motion or the presence of trophoblastic tissue on D&C. Thirty-nine of the initial randomized group were subsequently assessed for IVF, and the results of these cycles were also reported.
Main Outcomes Measured	Pregnancy before, during, and after treatment.
Main Results	Of 177 couples enrolled, 22 were excluded because of incomplete data, missed tablets or injections, patient withdrawal, or the presence of exclusion criteria that should have been picked up prior to randomization. Data from the remaining 155 patients with primary unexplained infertility were analyzed. Seven pregnancies occurred after enrolment but prior to treatment. Of the 148 couples left, all completed four cycles of treatment or achieved pregnancy. The mean age of female partners was 30 years and the mean duration of infertility was 4.3 years. Pregnancy data were as follows: Group 1 — placebo/placebo: 0/36 couples (0%) Group 2 — placebo/hCG: 4/36 couples (11%) Group 3 — clomiphene/placebo: 7/37 couples (19%) Group 4 — clomiphene/hCG: 3/39 couples (8%) If the individual treatment groups were compared with the placebo outcome using Fisher's exact test with Bonferroni's correction, only group 3 (CC/placebo) showed statistically significant improvement ($p < 0.04$). Eighteen pregnancies occurred during the six months following treatment, seven of these in the placebo/placebo group. Thirty-five couples went on to IVF. Despite identifying a significant number of male factor problems, six pregnancies occurred with a mean of 1.1 cycles of treatment (17% per couple).

Conclusions	The authors conclude that although spontaneous pregnancy occurs in unexplained infertility, CC appears to hasten this occurrence. However, they do not discuss the absence of pregnancies from the placebo/placebo group, a chance event that would not be expected based on a monthly fecundity of perhaps 3% in this patient group.

Authors and Year: C.M.A. Glazener et al. (1990)

Title	"Clomiphene Treatment for Women with Unexplained Infertility: Placebo-Controlled Study of Hormonal Responses and Conception Rates."
Objective	To determine the efficacy of CC versus placebo in unexplained infertility.
Design	Randomized crossover trial in 118 patients. They received treatment or placebo for three cycles before crossing over to the alternative approach.
Setting	University of Bristol, Centre of Reproductive Medicine, Bristol, United Kingdom.
Patients	Couples were included if the duration of infertility exceeded one year. Women all had normal menstrual cycles (21-35 d), serum prolactin, thyroid hormone levels, coital frequency, and post-coital testing. Laparoscopy was not done on all patients. One hundred and eighteen couples were treated. The median duration of infertility for these couples was 28 months.
Interventions	Clomiphene 100 mg on days 2-6 was given for three treatment cycles before crossing over to placebo — a matching pill given for the same duration.
Main Outcomes Measured	Serum progesterone; pregnancy.
Main Results	Luteal phase serum progesterone was higher with clomiphene than with placebo. Of 105 patients treated with placebo, 15 conceived (14%). Of 109 treated with clomiphene, 24 conceived (22%), including two sets of twins. Four patients failed to complete their second phase of treatment. Three-month cumulative conception rates correlated with duration of infertility and parity. In women with < 3 years' infertility, there was no significant difference between clomiphene and placebo, but in those with > 3 years' infertility, rates were 14.4% versus 2.9%, respectively. In women with a previous pregnancy, cumulative conception rates were 19.7% versus 7.8%. Female age had no appreciable effect on the cumulative pregnancy rate.

Conclusions	Clomiphene increases progesterone production in the luteal phase. An increased cumulative pregnancy rate was noted in women with > 3 years of infertility and secondary infertility.

Authors and Year: R.F. Harrison and R.R. O'Moore (1983)

Title	"The Use of Clomiphene Citrate With and Without Human Chorionic Gonadotropin."
Objective	To determine the efficacy of CC with and without hCG versus placebo in women with unexplained infertility.
Design	This was a two-arm randomized crossover trial. The method of randomization was not reported. Thirty couples received clomiphene for three cycles before being randomized to a combination of clomiphene and hCG versus placebo and hCG. Although crossover occurred after six months of treatment, results were reported separately for each treatment period.
Setting	Federated Dublin Voluntary Hospitals, Dublin, Ireland.
Patients	Thirty couples were recruited. The following tests were normal: semen analysis; post-coital test; HSG; laparoscopy; immunological tests; and plasma FSH, LH, estradiol (E_2), prolactin, and progesterone. The mean age of the women was 29.3 years, and the average duration of infertility was 5.4 years. Ten women had secondary infertility.
Interventions	1. Clomiphene 100 mg daily for 4 d beginning on cycle day 3. All patients received clomiphene alone for three cycles. 2. Clomiphene 100 mg daily for 4 d followed by hCG 5 000 IU on cycle day 12 of each cycle for a total of six cycles. 3. Placebo, one tablet for 4 d, days 3-6, followed by hCG 5 000 IU on day 12.
Main Outcomes Measured	Serum gonadotropins, progesterone, and prolactin; treatment side-effects; pregnancy; spontaneous abortion.
Main Results	There were no differences in mean gonadotropin, estradiol, progesterone, or prolactin levels between groups. No significant side-effects were noted during the study, although three patients dropped out during their second six months. One patient had a cerebral haemorrhage while on placebo and hCG, a second experienced severe depression, and a third adopted a child. No pregnancies were achieved during the three-month pre-randomization period on clomiphene alone. Five pregnancies were achieved with clomiphene + hCG, three during the first and two during the second treatment periods. One pregnancy was achieved in the placebo hCG group during the second treatment period. A log-rank test showed a z value equal to 1.76, $p < 0.1$. There was no significant difference in

mean female age between pregnant and non-pregnant subjects. However, the mean duration of infertility was significantly less (3.3 years) in pregnant women than in non-pregnant women (6 years).

Conclusions — The authors suggest that clomiphene alone is of no value and, indeed, may have an anti-fertility effect. They point out a non-significant trend toward an improved pregnancy rate using clomiphene + hCG. Thus, the authors conclude that this combination may be beneficial. They draw attention, however, to the shorter duration of infertility in patients during this trial.

Authors and Year: C.A. Iffland, R.W. Shaw, and J.L. Beynon (1989)

Title — "Is Danazol® a Useful Treatment in Unexplained Primary Infertility?"

Objective — To determine whether Danazol® significantly improves the pregnancy rate in couples with unexplained primary infertility.

Design — Randomized, double-blind, placebo-controlled study. Method of randomization was not described.

Setting — Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, London, and Royal West Sussex Hospital, Chichester, United Kingdom.

Patients — Included were 39 patients aged 20-38 years with primary unexplained infertility. The definition of unexplained infertility was based on regular ovulation confirmed by mid-luteal progesterone, normal laparoscopy at least six months prior to entering the study, a normal post-coital test, and normal semen analysis, i.e., density > 20×10^6/mL, motility > 40%, abnormal forms < 50%, agglutination < 10%, and white blood cells < 1×10^6/mL. Varicocele was also absent. The mean duration of infertility in the current study was 4.8 years in the placebo group and 5.8 years in the Danazol® group. Mean female ages were 30.8 and 30.9 years respectively.

Interventions — Danazol® 200 mg PO for 100 d commencing on the first day of the menstrual cycle. Matching placebo capsules were given one per day for 100 d.

Main Outcomes Measured — Haematologic parameters; liver function tests; pregnancy.

Main Results — Eight patients were excluded, six because they failed to start or complete treatment and two because of biochemical abnormalities on blood testing. All seventeen patients receiving placebo and 11 of the 14 receiving Danazol® completed treatment. This suggests that although side-effects were reported with a similar frequency between groups, they may have been more severe in the Danazol® group. Groups were similar in terms of age and duration of infertility. One patient

	in the placebo group conceived six months post-treatment; none conceived in the Danazol® group. The follow-up period after treatment was 12 months. Haemoglobin level, packed cell volume, and red blood cell count were higher in the Danazol® group. Liver function tests were not affected. There were significant increases in weight and blood pressure in the Danazol® group. Skin changes, menstrual disturbances, and feelings of weight gain were equally common in both groups.
Conclusions	The prognosis for couples with long-standing primary unexplained infertility is poor, and Danazol® does not affect the outcome. The positive findings of Greenblatt et al. (1974) and vanDijk et al. (1979) were explained on the basis of patient selection.

Authors and Year: C.A. Kirby et al. (1991)

Title	"A Prospective Trial of Intrauterine Insemination of Motile Spermatozoa Versus Timed Intercourse."
Objective	To determine the efficacy of IUI in couples with abnormal cervical mucus, male factor, and unexplained infertility.
Design	This was a two-arm crossover trial alternating treatments between IUI and timed vaginal intercourse. Patients were randomly allocated to either treatment group for their first cycle. The method of randomization was not described.
Setting	Reproductive Medicine Centre, The University of Adelaide, The Queen Elizabeth Hospital, Woodville, South Australia, Australia.
Patients	All couples had a duration of infertility of greater than two years. All males, except those in the abnormal sperm group, had a semen analysis showing concentration $> 40 \times 10^6$/mL sperm, progressive motility > 45%, and normal morphology > 40% (15th percentile for reference population of semen donors). Tubal patency was assessed by laparoscopy. Cervical mucus was considered to be abnormal if the pH was < 6 or if the amount of mucus was considered to be abnormal. Patients with anti-sperm antibodies were excluded. Moderate semen defect was classified as $10\text{-}40 \times 10^6$/mL sperm, 30-45% progressive motility, and 30-40% normal morphology. Severe sperm defect was classified as less than 10×10^6/mL sperm, < 30% progressive motility, and < 30% normal morphology. The lower limit for inclusion was the retrieval of > 100 000 motile sperm after preparation. Between 1983 and 1988, a total of 295 couples were enrolled, undergoing 600 IUI cycles and 505 timed intercourse cycles.
Interventions	IUI with either swim-up or percoll-prepared sperm.
Main Outcomes Measured	Pregnancy.

Main Results	Considering the first treatment cycle alone, 9/226 cycles (4%) resulted in pregnancy following intercourse versus 27/266 cycles (10.2%) following IUI. When all cycles were considered, the pregnancy rate per cycle was 3.4% following intercourse versus 6.2% following IUI (log-rank test, $p = 0.05$). When considering diagnostic groups, a significant improvement was noted with severe male factor patients, 2/154 (1.3%) versus 10/179 (5.6%) ($p < 0.05$), following intercourse and IUI, respectively. In the unexplained infertility group, pregnancy rates were similar between groups (2.4 and 4.1% following intercourse and IUI, respectively). In the mucus hostility group, the results were 4/51 (7.8%) versus 7/58 (12.1%). In the moderate semen defect group, the results were 8/177 (4.5%) versus 14/218 (6.4%) following intercourse and IUI, respectively.
Conclusions	IUI appears to be of benefit in the subgroup of patients with severe male factor infertility. It also appears to be more effective in the first treatment cycle than in subsequent treatment cycles. These results do not bear out the extremely high (20%) pregnancy rate per cycle published in this group's preliminary report (Kerin et al. 1984).

Authors and Year: J. Leeton et al. (1987)

Title	"A Controlled Study Between the Use of Gamete Intrafallopian Transfer (GIFT) and In Vitro Fertilization and Embryo Transfer in the Management of Idiopathic and Male Infertility."
Objective	To determine the efficacy of GIFT versus IVF and ET in the management of idiopathic and male infertility.
Design	This was a two-arm quasi-randomized study with crossover. Patients were allocated in an alternate fashion to either IVF or GIFT and, if unsuccessful, were switched to the alternate treatment for their second attempt.
Setting	Monash University/Epworth In Vitro Fertilization Centre, Epworth Medical Centre, Melbourne, Victoria, Australia.
Patients	This study involved patients with idiopathic and male factor infertility. The average age of female GIFT patients was 32.6 years and of IVF patients was 33 years. Mean durations of infertility were similar (6.2 versus 6.7 years, respectively). Idiopathic infertility was defined on the basis of normal laparoscopy, normal hormonal ovulatory profiles with luteal phase adequacy by endometrial biopsy, and normal semen analysis. Male factor infertility was defined by a sperm count of $< 20 \times 10^6$/mL sperm, but normal motility (> 40%) and morphology (> 40% normal forms).
Interventions	GIFT and IVF.

Main Outcomes Measured: Pregnancy.

Main Results: Eight patients randomized to GIFT were switched to IVF because of technical difficulties at laparoscopy. There were no significant differences between pregnancy following IVF and GIFT for either diagnostic group:

	GIFT	IVF
Idiopathic	7/45 (15.6%)	6/30 (20%)
Male factor infertility	2/7 (28.6%)	2/7 (28.6%)

Conclusions: This study is of limited power, but demonstrates no significant difference between IVF and GIFT in idiopathic and non-severe male factor infertility.

Authors and Year: J.C. McBain and R.J. Pepperell (1982)

Title: "Use of Bromocriptine in Unexplained Infertility."

Objective: To evaluate the place of bromocriptine in the treatment of women with unexplained or poorly explained infertility.

Design: Double-blind, randomized crossover trial comparing bromocriptine 2.5 mg BID with placebo. Patients were observed for one month prior to commencing treatment. Randomization was by pharmacy (tablets identical). Where a pregnancy had not occurred after three cycles of treatment with the first agent, the other agent was administered for an additional three cycles. Patient compliance was determined by counting the number of tablets left at the end of each cycle.

Setting: Department of Obstetrics and Gynaecology, University of Melbourne, Australia.

Patients: Fifty women were included according to the following criteria: ≥ 2 years infertility (mean 4.8 years); ovulation regular; post-coital test normal at mid-cycle; husband's semen analysis showed Eliasson index of ≤ 10; and laparoscopy normal with patent tubes and no endometriosis. Thirty-nine women had primary infertility and 11 had secondary infertility.

Interventions: Bromocriptine 2.5 mg BID.

Main Outcomes Measured: Total urinary estrogen and pregnanediol; serum prolactin; clinical pregnancy.

Main Results: Five women conceived during the observation cycle, four during placebo treatment, and four with bromocriptine. Another five women conceived within the 12-month follow-up after treatment had finished. There was no difference between

pregnant and non-pregnant groups in terms of serum prolactin level. There was no evidence of occult pregnancy loss based on hCG measurement prior to menstruation in either treatment group.

Conclusions — There was no evidence that pregnancies occurring during this trial were the result of treatment. There was no evidence of occult pregnancy wastage in this patient group.

Authors and Year: A.R. Martinez et al. (1990)

Title — "Intrauterine Insemination Does and Clomiphene Citrate Does Not Improve Fecundity in Couples with Infertility due to Male or Idiopathic Factors: A Prospective, Randomized, Controlled Study."

Objective — To determine whether IUI and/or CC are advantageous in the treatment of infertility attributed to male factor or cervical factor, or infertility of unknown origin.

Design — Patients were randomized to receive a sequence of four treatment approaches. There were eight balanced sequences for these treatments. The method of randomization was not described.

Setting — University Hospital, Amsterdam, Netherlands.

Patients — Forty couples were asked to participate. These included 21 couples with idiopathic infertility based on normal semen analysis, a post-coital test, screening for sperm agglutinating antibodies, an endometrial biopsy, an HSG, and diagnostic laparoscopy. Cervical factor infertility was suspected based on abnormal post-coital testing in two couples. In the remaining 17 couples, a male factor was noted: sperm counts of 5-20 million/mL in which 30% or less of the sperm had a qualitative motility score of < 60%.

Interventions

1. 100 mg of clomiphene, days 3-7, followed by IUI.
2. Clomiphene as above followed by timed intercourse.
3. IUI in a spontaneous cycle.
4. Timed intercourse in a spontaneous cycle. Timing of insemination or intercourse was based on urinary LH testing. Patients were also monitored with daily ultrasound. Sperm were prepared for insemination using a two-layer percoll gradient. A Makler device was used for insemination. Detection of pregnancy was by quantitative ßhCG in urine 14 d after insemination and in serum one week after a missed period.

Main Outcomes Measured — Pregnancy.

Main Results	Data from 132 cycles were analyzed from a possible 160 in the study design. Nine patients conceived. Five were in the clomiphene + IUI group, one in the clomiphene intercourse group, three in the IUI natural cycle group, and none in the intercourse natural cycle group. When combining data for IUI versus timed intercourse, a significant improvement was demonstrated (Mantel-Haenszel test, $p < 0.02$). When data were combined comparing clomiphene with other cycles, no significant difference was demonstrated. When idiopathic infertility patients were examined separately, no significant difference was demonstrated between treatment groups (3/33 versus 1/35, IUI versus intercourse).
Conclusions	These data are presented in a way that does not allow for analysis by individual treatment group. Approximately half of the IUI and intercourse cycles also involved CC, but data are not reported for each subgroup. Although the authors' conclusion supports the use of IUI in this general population, the sequential design and unorthodox analysis are potentially biased and the results, therefore, should be treated with caution.

Authors and Year: J.C. Nulsen, S. Dumez, and D.A. Metzger (1990)

Title	"Randomized Prospective Trial of Pergonal (hMG) Superovulation with Intrauterine Insemination (IUI) versus IUI Alone."
Objective	To compare the efficacy of hMG + IUI with IUI alone in patients with infertility-attributed endometriosis, male factor, or no obvious cause.
Design	This was a two-arm crossover trial with random allocation to the first treatment cycle.
Setting	Division of Reproductive Endocrinology and Infertility, University of Connecticut Health Center, Farmington, Connecticut.
Patients	One hundred and ten couples with long-standing infertility were enrolled. Infertility investigation included endometrial biopsy, semen analysis, HSG, a post-coital test, and, in most cases, diagnostic laparoscopy.
Interventions	hMG + IUI versus IUI alone. hMG treatment began on day 3 or 4, using two to three ampoules daily. hCG was administered when two or more follicles reached 16 mm in diameter associated with an estradiol level of 200 pg/mL per follicle. IUI was performed 36 h later.
Main Outcomes Measured	Pregnancy.

Main Results

	hMG/IUI	IUI	
Unexplained infertility	9/32 (28%)	0/25 (0%)	$p < 0.01$
Endometriosis	13/81 (16%)	1/60 (2%)	$p < 0.01$
Male factor	8/46 (17%)	1/31 (3%)	$p < 0.13$

Conclusions

This study suggests that hMG + IUI is superior to IUI alone in the treatment of unexplained infertility and endometriosis. Note: These data come from an abstract, and methodological criteria cannot be evaluated.

Authors and Year: P.F. Serhal et al. (1988)

Title

"Unexplained Infertility — The Value of Pergonal® Superovulation Combined with Intrauterine Insemination."

Objective

To compare conception rates in couples with unexplained infertility undergoing hMG superovulation alone, IUI alone, or a combination of both treatments.

Design

Retrospective cohort study.

Setting

Department of Obstetrics and Gynaecology, University College and Middlesex School of Medicine, London, United Kingdom.

Patients

All had previously undergone routine infertility screening demonstrating normal semen analysis by WHO criteria, normal post-coital tests, a biphasic body temperature chart, luteal phase length ≥ 12 days, luteal progesterone ≥ 35 nmol/L, and normal laparoscopy, with normal FSH/LH prolactin and ovarian ultrasound. Fifteen women received IUI alone (group 1), 25 received superovulation alone (group 2), and 22 received superovulation + insemination (group 3). Seven group 3 patients received both IUI and DIPI.

Interventions

IUI involved swim-up preparation in Ham's F-10 medium. Three hundred microlitres of sperm in suspension were injected into the uterus on one occasion 32-36 h after hCG injection. hMG was administered in a standard protocol, using three ampoules IM beginning on days 2 or 3, followed by serial ultrasound scanning beginning on day 8. Pergonal® injections were adjusted according to the patient's response and continued until 2-5 dominant follicles ≥ 17 mm in diameter were noted.

In patients receiving DIPI, the posterior fornix was sprayed with 10% xylocaine 10 min before the procedure. Sperm were then drawn into a 2-mL syringe and injected via a 22-gauge spinal needle into the pouch of Douglas. All patients received luteal phase support in the form of vaginal progesterone suppositories 400 mg BID or dydrogesterone 10 mg TID PO.

Main Outcomes Measured	Clinical pregnancy.
Main Results	IUI alone: 1/30 cycles (15 couples). hMG alone: 3/49 cycles (25 couples). hMG + IUI: 6/19 cycles (15 couples). hMG + IUI + DIPI: 3/15 cycles (7 couples). Six of the nine women achieving pregnancy following Pergonal® and IUI ± DIPI had single pregnancies; two had multiple pregnancies. There was one clinical abortion.
Conclusions	These data suggest a significant improvement in the pregnancy rate with a combination of hMG + IUI/DIPI versus IUI alone ($\chi^2 = 4.83$, $p < 0.05$) or hMG alone ($\chi^2 = 4.9$, $p < 0.05$). However, there were significant differences between groups in terms of the distribution of primary and secondary infertility and in terms of age and duration of infertility, which undermine these conclusions.

Authors and Year: J.G. vanDijk et al. (1979)

Title	"The 'Treatment' of Unexplained Infertility with Danazol®."
Objective	To determine the efficacy of Danazol® compared with placebo in unexplained infertility.
Design	Randomized controlled study of 40 women with unexplained infertility. Method of randomization was not described.
Setting	Department of Obstetrics and Gynaecology and Chemical Pathology, Lyden University Medical Centre, Lyden, Netherlands.
Patients	Patients were included according to the following criteria: ovulatory menstrual cycles as judged by basal body temperature and satisfactory luteal plasma progesterone levels; normal sperm count and motility; a positive post-coital test; and normal HSG and laparoscopy. Only women who had laparoscopy at least six months previously were eligible for this study. Median ages in the placebo and Danazol® groups were 29.5 and 30 years, respectively. Median durations of infertility were 5.5 and 6 years, respectively.
Interventions	The treatment group received Danazol® 200 mg daily for 100 d. The control group received a placebo tablet for 100 d, starting on the first day of menstruation.
Main Outcomes Measured	Serum gonadotropins, prolactin, estradiol, progesterone, and testosterone; clinical pregnancy.
Main Results	Gonadotropin levels were not affected by Danazol® treatment. Mean serum progesterone dropped from 8.1 to 0.5 ng/mL. Mean serum estradiol and estrone concentrations decreased significantly up to the eighth week of treatment. The mean

serum testosterone level was unchanged. Twelve of the Danazol® group became oligomenorrhoeic and six amenorrhoeic, whereas three maintained regular cycles. Moderate weight gain and a slight increase in blood pressure were common. Approximately half of the women complained of breast tenderness in the Danazol® group. Side-effects disappeared post-treatment.

Five women conceived in the Danazol® group (n = 21). None conceived during the six-month follow-up period in the placebo group (n = 19). However, one patient conceived during the "treatment period" in the placebo group, and she was excluded from further analysis. Had she been included, the difference in pregnancy rates between groups, which was reported as being statistically significant ($\chi^2 = 4.91$, $p < 0.05$), would not have reached this level ($\chi^2 = 1.1$).

Conclusions

The authors conclude that Danazol® is an effective treatment for unexplained infertility, but the mechanisms of action are not clear. Their conclusions are tenuous at best, however, and invalid if the analysis is repeated to include the single pregnant patient in the placebo group.

Authors and Year: S. Welner, A.H. DeCherney, and M.L. Polan (1988)

Title

"Human Menopausal Gonadotropins: A Justifiable Therapy in Ovulatory Women with Long-Standing Idiopathic Infertility."

Objective

To determine whether couples with "unexplained infertility" on an IVF waiting list have an increased conception rate following empirical hMG therapy versus no treatment.

Design

This appears to be a prospective cohort study. The mean time between being placed on the IVF waiting list and receiving treatment was six months. Pregnancies occurring during empirical hMG treatment and spontaneous pregnancies in the control group were recorded. Spontaneous pregnancies in the treatment group were also noted. Finally, all patients subsequently undergoing IVF were evaluated in terms of their outcome.

Setting

Department of Obstetrics and Gynecology, Yale University School of Medicine, New Haven, Connecticut.

Patients

Inclusion criteria: biphasic basal temperature charts; in-phase late luteal endometrial biopsy; post-coital tests with clear mucus and > 5 motile sperm per high-power field; semen analysis normal by WHO criteria; and HSG with at least one patent tube and laparoscopy with at least one visibly normal tube. It should be noted, however, that 60% of the couples in the treatment group had previously undergone tubal or

	endometriosis surgery. Entry into treatment (n = 97) and control (n = 48) groups was determined by patient and physician preference.
Interventions	Beginning on day 3, two ampoules of Pergonal® were administered. Monitoring began on day 8 and continued twice daily using serum estradiol alone. Ultrasound was not used for routine monitoring. Up to four treatment cycles were given (n = 97 cycles).
Main Outcomes Measured	Pregnancy, miscarriage, and live birth. Endocrine response to hMG was also noted.
Main Results	A total of 12 conceptions occurred among the 97 couples undergoing empirical hMG treatment (12.4%). Eight of these reached term (8.2%). Seven of 89 patients in the same group who subsequently underwent IVF achieved pregnancies (12% per cycle), although the number of IVF treatment cycles is not reported. Later in the discussion, it appears that couples underwent one cycle of IVF each. There were no differences in endocrine response between conception and non-conception cycles. In the control group of 48 couples not receiving hMG, two pregnancies occurred during the approximately six-month-long period prior to IVF treatment (4%, p = 0.07). When normal infertile couples with no previous pelvic surgery were considered, 3/39 couples conceived with hMG versus 2/48 in the control group.
Conclusions	This study is difficult to interpret because its population includes unexplained infertility, surgically corrected tubal disease, and endometriosis. Also, in terms of follow-up, the empirical hMG group received four cycles of treatment, the control group probably six cycles of observation, and the IVF group probably only one cycle of treatment. The results were reported in a way that suggests that all of the follow-up periods were of similar duration. Clearly, this is not the case. No significant difference was demonstrated between treatment versus no treatment.

Authors and Year: C.S. Wright, S.J. Steele, and H.S. Jacobs (1979)

Title	"Value of Bromocriptine in Unexplained Primary Infertility: A Double-Blind Controlled Trial."
Objective	To determine the efficacy of bromocriptine in patients with unexplained primary infertility.
Design	Randomized double-blind trial of 47 women with unexplained primary infertility receiving either bromocriptine 2.5 mg BID or placebo. Bottles containing bromocriptine or placebo were

	numbered in random order and supplied by Sandos Products Ltd. Follow-up was at three and six months after treatment.
Setting	St. Mary's Hospital Medical School, London. United Kingdom
Patients	Inclusion criteria: primary infertility ≥ 2 years; regular menses under six weeks' duration; biphasic temperature chart; duration of luteal phase > 10 d; serum progesterone on days 18-21 > 25 nmol/L; tubal patency established by laparoscopy or HSG; normal post-coital test; and husband sperm count > 20×10^9/L. Mean female ages in the bromocriptine and placebo groups were 30.8 and 30.4 years, respectively. Mean durations of infertility were 4.82 and 4.81 years.
Interventions	Bromocriptine 2.5 mg BID versus placebo.
Main Outcomes Measured	Serum prolactin, progesterone, and estradiol concentrations; clinical pregnancy; duration of menstrual cycle phases.
Main Results	There were no significant differences between the 24 patients receiving bromocriptine and the 23 receiving placebo with respect to age, duration of infertility, or husband's sperm quality. There was a small but significant difference in baseline serum prolactin concentrations between the two groups, a slightly lower value being found in the group treated with bromocriptine. Five women became pregnant during treatment with placebo and seven during treatment with bromocriptine. Life-table analysis revealed no significant difference between the two groups. In patients taking bromocriptine, serum prolactin concentrations fell below 2 µg/L in all but two patients. There was a small but significant decrease in serum prolactin concentration in the placebo group. No change occurred in progesterone or estradiol concentrations. Side-effects were similar between placebo and treated groups in terms of nausea, dizziness, and headaches. The mean age of the 12 patients who became pregnant during the trial was significantly less than that of the 35 women who did not conceive (28.9 versus 31.5, $p < 0.001$). Also, the conception group had a shorter mean duration of infertility (3 versus 5.3 years, $p = 0.007$).
Conclusions	Bromocriptine does not improve the rate of conception in patients with unexplained primary infertility. Age and duration of infertility are important prognostic factors in these patients. Side-effects from bromocriptine and placebo were similar.

Authors and Year: J.L. Yovich and P.L. Matson (1988)

Title	"Early Pregnancy Wastage After Gamete Manipulation."
Objective	To evaluate pregnancy outcomes associated with five fertility treatments.

Design	Patient records at a private fertility clinic over a five-year period.
Setting	Perth IVF-ET Centre, Perth, Australia.
Patients	852 women were included.
Interventions	1. artificial insemination with husband's sperm (AIH): sperm were prepared using a swim-up technique with Ham's-F10 or Tyrode-based culture media. 2. artificial insemination with donor sperm (AID): intracervical insemination of frozen donor sperm was used. 3. IVF-ET: ovulation induction consisted of CC and hMG. Laparoscopic or transvaginal ultrasound-guided oocyte retrieval was performed. 4. GIFT: all of these procedures were laparoscopic. 5. pronuclear oocyte salpingo transfer (PROST): in this modification of the GIFT technique, pronuclear embryos were transferred into the fallopian tube at laparoscopy.
Main Outcomes Measured	Biochemical pregnancy, missed abortion, spontaneous abortion, ectopic pregnancy, delivery beyond 20 weeks.
Main Results	The mean early pregnancy wastage ranged from 18% following donor insemination to 32% following IVF-ET. These differences did not reach statistical significance. Similar numbers of missed abortions occurred between groups, ranging from 7.9% following GIFT to 19.7% following AIH. Ectopic pregnancy was less common following donor insemination (0.9% versus 9.2% following GIFT).
Conclusions	Although the authors state that "their findings confirm a high pregnancy wastage rate in subfertile women and highlight deficiencies in sperm separation, gamete handling and IVF-ET culture techniques," their data do not fully support this statement. In control groups of 462 women conceiving without gamete manipulation and 175 following clomiphene or hMG, similar ongoing pregnancy rates were encountered (75.3% and 69.7%, respectively).

Appendix 2. Structured Abstracts — Controlled Trials in Endometriosis-Related Infertility

Authors and Year: S.Z.A. Badawy et al. (1988)

Title	"Cumulative Pregnancy Rates in Infertile Women with Endometriosis."

Objective	To compare pregnancy rates following Danazol® or no treatment for mild endometriosis.
Design	A three-arm retrospective cohort study with a six-month treatment of Danazol® or expectant management or conservative surgery.
Setting	State University of New York, Health Sciences Center at Syracuse, Syracuse, New York.
Patients	All women presenting with endometriosis and infertility were included. Mean female age in the expectant group was 30.3 years and in the Danazol® group was 28.7 years.
Interventions	Patients were treated with Danazol® 800 mg/d for six months, were followed expectantly, or underwent conservative surgery.
Main Outcomes Measured	Pregnancy.
Main Results	Sixteen of 38 patients who were managed with Danazol® therapy achieved pregnancy. This is in contrast to 9/14 patients who were offered expectant management. These results were not statistically significant. Five-year cumulative pregnancy rates were also reported. These were 90% with no treatment versus 89% following surgery.
Conclusions	In minimal to moderate degrees of endometriosis, expectant therapy should be used for 6-12 months, as there is no obvious benefit from Danazol® therapy.

Authors and Year: S.R. Bayer et al. (1988)

Title	"Efficacy of Danazol® Treatment for Minimal Endometriosis in Infertile Women: A Prospective, Randomized Study."
Objective	1. Compare pregnancy rates in a large population of Danazol®-treated and untreated patients with minimal endometriosis. 2. Extend the period of observation from 6 to 12 months. 3. Analyze the data using life-table analysis.
Design	This was a two-arm randomized study with treatment allocation by a randomly selected card to either no treatment or treatment with decreasing doses of Danazol® over a six-month period. Patients were then observed for an additional 12 months with pregnancy being the outcome of interest.
Setting	Beth Israel Hospital, Harvard Medical School, Boston, Massachusetts.
Patients	Patients with laparoscopically determined minimal endometriosis with tubal patency were included. Thirty-seven

	patients were allocated to Danazol® treatment and 36 patients were managed expectantly.
Interventions	Danazol®, at a dose of 800 mg daily for the first two months, 600 mg daily for the next two months, and 400 mg daily for the final two months, was used in the treatment group. All patients were then observed for an additional 12 months. The control group was observed for the 12 months following laparoscopy.
Main Outcomes Measured	Clinical pregnancy rates were determined for each group. Patients lost to follow-up were accounted for using life-table techniques.
Main Results	Thirteen of 37 patients treated with Danazol® and 17 of 36 untreated patients conceived. At the end of the 12-month period, the cumulative pregnancy rate was 37.2 ± 8.4% in the Danazol® group and 57.4 ± 10.4% in the untreated group (z value = 1.15, $p > 0.10$).
Conclusions	Danazol® is not an effective treatment for infertility associated with minimal endometriosis.

Authors and Year: V.C. Buttram, R.C. Reiter, and S. Ward (1985)

Title	"Treatment of Endometriosis with Danazol®: Report of a Six-Year Prospective Study."
Objective	1. To compare an 800-mg regime of Danazol® with a 400-mg regime with regard to side-effects, resolution of disease, and enhancement of conception rates. 2. To compare pregnancy rates in patients receiving Danazol® alone or in conjunction with surgery with pregnancy rates in patients receiving conservative surgery only.
Design	A triple-arm prospective cohort study comparing Danazol® alone, Danazol® for six months followed by surgery, or Danazol® for six months post-operatively.
Setting	Baylor College of Medicine, Texas Medical Center, Houston, Texas.
Patients	Two hundred and twenty infertile patients with laparoscopically confirmed endometriosis were included. Patients were classified according to the severity of disease as determined by the Acosta, AFS, and R-AFS classifications.
Interventions	Danazol® 800 mg/d or 400 mg/d was given either alone for a six-month period, pre-operatively for a six-month period, or post-operatively for a six-month period.
Main Outcomes Measured	Pregnancy rates based on the severity of endometriosis were calculated. In addition, side-effects associated with Danazol® administration were documented.

Main Results	Pregnancy rates were slightly higher for the 800-mg Danazol® regime than for the 400-mg regime. In patients with mild disease, the use of Danazol® alone resulted in pregnancy rates lower than those achieved with conservative surgery alone. Its use pre-operatively for all stages of disease resulted in a slightly higher pregnancy rate than when conservative surgery alone was employed. Danazol® was less effective when used post-operatively.
Conclusions	Although trends were determined, the small sample size failed to show any statistically significant differences in pregnancy rates among regimes. The side-effects of Danazol® were, however, shown to be significant, with 7% of patients discontinuing therapy because of them.

Authors and Year: A.P. Chong, M.E. Keene, and N.L. Thorton (1990)

Title	"Comparison of Three Modes of Treatment for Infertility Patients with Minimal Pelvic Endometriosis."
Objective	To address three modes of managing minimal pelvic endometriosis in patients suffering from infertility.
Design	A retrospective cohort study of a group of patients with laparoscopically diagnosed endometriosis and complaining of infertility. All patients had AFS classification Stage I disease.
Setting	University of Connecticut School of Medicine, Farmington, Connecticut.
Patients	One hundred and sixty-seven presenting with Stage I pelvic endometriosis over a six-year period were reviewed.
Interventions	Patients had been treated with Danazol® at varying doses, CO_2 laser, or a combination of CO_2 laser and Danazol®.
Main Outcomes Measured	Clinical pregnancy.
Main Results	Patients receiving Danazol® alone achieved a 48.9% pregnancy rate (23/47), patients undergoing CO_2 laser vaporization alone had a 44.6% pregnancy rate (37/83), and those receiving both CO_2 laser and Danazol® achieved a 51.4% pregnancy rate (19/37).
Conclusions	There was no statistically significant difference noted among different treatment modalities and the pregnancy rate.

Authors and Year: W.P. Dmowski et al. (1989)

Title	"Ovarian Suppression Induced with Buserelin or Danazol® in the Management of Endometriosis: A Randomized, Comparative Study."

Objective	To compare the efficacy of two methods of ovarian suppression in the management of endometriosis.
Design	A three-arm randomized study (method of allocation not described) for a period of six months involving 36 women with laparoscopically diagnosed endometriosis.
Setting	Department of Obstetrics and Gynecology, Grant Hospital of Chicago, Chicago, Illinois.
Patients	Patients with a diagnosis of infertility and a laparoscopic diagnosis of pelvic endometriosis were included. Mean female age was 30.8 years, and mean duration of infertility was 39.5 months.
Interventions	Patients were allocated to receive buserelin 1.2 mg IN, buserelin 0.2 mg SC, or Danazol® 800 mg daily for a six-month treatment period. All patients were subsequently followed for 12 months after completion of therapy.
Main Outcomes Measured	Pelvic pain scores; endometriosis scores; post-treatment pregnancies.
Main Results	There was a significant difference between pre- and post-treatment pain scores and the amount of endometriosis visible in both groups. Conception rates of 60% in the IN buserelin group, 25% in the SC buserelin group, and 63% in the Danazol® group were noted 12 months post-treatment. General and hypoestrogenic side-effects were similar in all groups, while androgenic and anabolic side-effects were more common with Danazol®.
Conclusions	Buserelin in the reported doses suppresses pituitary and ovarian functions to the same degree as Danazol®, with resultant clinical improvements and regression of endometriotic lesions being comparable. No significant difference in pregnancy rates was noted.

Authors and Year: J.A. Fayez, L.M. Collazo, and C. Vernon (1988)

Title	"Comparison of Different Modalities of Treatment for Minimal and Mild Endometriosis."
Objective	To study the resolution of endometriosis and effect on conception rate of operative laparoscopy or laparoscopy and Danazol® versus Danazol® alone.
Design	A three-arm prospective cohort study. Treatment allocation enhanced over 4.5 years from Danazol® (18 months) to Danazol® and surgery (18 months) to surgery alone (18 months). Follow-up was for 12 months in each group.
Setting	Bowman Gray School of Medicine, Winston-Salem, North Carolina.

Patients	Patients with minimal or mild endometriosis were divided into the three arms of the study.
Interventions	Patients received operative laparoscopy with excision of implants, operative laparoscopy, and Danazol® 800 mg/d for six months, or Danazol® alone for six months.
Main Outcomes Measured	Clinical pregnancy rate; resolution of endometriosis.
Main Results	Twenty of 76 (26%) patients treated with Danazol® alone conceived. This compared with 43/80 (54%) patients treated with a combination of operative laparoscopy and Danazol®. Of those patients treated with operative laparoscopy alone, 60/82 (73%) patients conceived. Complete resolution of endometriosis was noted in 75% of patients treated with a combination of laparoscopy and Danazol® and 85% of those patients treated with operative laparoscopy alone.
Conclusions	The pregnancy rate was significantly higher in those patients treated with operative laparoscopy alone when compared with the other two groups.

Authors and Year: L. Fedele et al. (1989a)

Title	"Gestrinone Versus Danazol® in the Treatment of Endometriosis."
Objective	To compare the efficacy of gestrinone with that of Danazol® in two comparable groups of infertile patients with endometriosis.
Design	A two-arm randomized study (method of allocation not described).
Setting	University of Milan, Milan, Italy.
Patients	Thirty-nine infertile women with a laparoscopic diagnosis of endometriosis were recruited. Patients with bilateral tubal disease were excluded. R-AFS Stages I-IV were included. Mean female age was 29.8 years and mean duration of infertility was 49-56 months.
Interventions	Six months of treatment with either gestrinone 2.5 mg twice per week or Danazol® 600 mg daily.
Main Outcomes Measured	Hormonal levels along with side-effects; clinical pregnancy.
Main Results	No significant differences were found between drugs and side-effects. Similarly, the 30% (6/20) pregnancy rate noted in the group treated with gestrinone was not significantly different from the 37% (7/19) pregnancy rate observed in the group treated with Danazol®.
Conclusions	Neither gestrinone nor Danazol® appeared to confer improved benefit in the infertility-directed treatment of endometriosis.

Authors and Year: L. Fedele et al. (1989b)

Title	"Buserelin Versus Danazol® in the Treatment of Endometriosis-Associated Infertility."
Objective	The aim of this study was to analyze prospectively the clinical results and side-effects of Gn-RHa (buserelin) and Danazol® in two comparable groups of infertile patients with endometriosis.
Design	A two-arm randomized study (method of randomization not described).
Setting	University of Milan, Milan, Italy.
Patients	Sixty-two patients with laparoscopically diagnosed endometriosis associated with infertility were included. Patients with bilateral tubal occlusion or whose partner had severe dyspermia were not admitted to the study. Mean female age was 30.2 years, and mean duration of infertility was 39-45.2 months.
Interventions	Patients received either 400 µg of IN buserelin TID or 200 mg of Danazol® tablets TID. The treatment was started within the first 3 d of the cycle and was continued for six months in both groups. Both groups were followed for 12 months after termination of treatment.
Main Outcomes Measured	Frequency of dysmenorrhoea, pelvic pain, and dyspareunia; change in laparoscopic findings; side-effects; cumulative pregnancy rates.
Main Results	Both treatments demonstrated improvement in pain symptomatology and reduction in the extent of disease at repeat laparoscopy. Cumulative pregnancy rates of 48% in the buserelin group and 43% in the Danazol® group were comparable. Fewer side-effects were noted with buserelin.
Conclusions	The effectiveness of buserelin in the treatment of endometriosis was similar to that of Danazol®. No appreciable difference in fertility was documented. Buserelin appears to be better tolerated.

Authors and Year: D. Federici et al. (1988)

Title	"Endometriosis and Infertility: Our Experience over Five Years."
Objective	To report on five years of experience in managing infertile women affected by genital endometriosis.
Design	A retrospective cohort study comparing Danazol®, conservative surgery and Danazol® therapy, and expectant management.
Setting	University of Milan, Milan, Italy.
Patients	One hundred and sixty-three patients diagnosed as having endometriosis accompanied by infertility over a five-year period

	were included. Patients were allocated to the different therapeutic modalities in an unselected fashion. Patients with co-existing infertility factors were not excluded.
Interventions	One hundred and twenty patients were treated with Danazol® 600 mg daily for a period of four to six months. Twenty-eight patients had conservative surgical treatment associated with Danazol® therapy. Fifteen women had no therapy and were followed by expectant management.
Main Outcomes Measured	Clinical pregnancy.
Main Results	A pregnancy rate of 39% was noted in those patients treated with surgery and Danazol® therapy. This compared with a rate of 28% in those treated with Danazol® alone.
Conclusions	There was no statistically significant difference in fertility rates in those patients treated with the two described methods. However, duration of follow-up was not stated.

Authors and Year: C.R. Garcia and S.S. David (1977)

Title	"Pelvic Endometriosis: Infertility and Pelvic Pain."
Objective	The purpose was to review the most recent experience with endometriosis and fertile patients at a single hospital.
Design	A cohort study of patients to whom surgery was either recommended or not recommended. Patients were followed for a period of 24 months.
Setting	University of Pennsylvania, Philadelphia, Pennsylvania.
Patients	All patients presenting for treatment of infertility secondary to endometriosis over a 10-year period were included. A total of 119 women were reviewed.
Interventions	Surgery was recommended to 86 women and not recommended to 33 women. Five women in the latter group were insistent on surgery.
Main Outcomes Measured	Clinical pregnancy; the prevalence of dysmenorrhoea and dyspareunia.
Main Results	A total pregnancy rate of 32.4% was documented in patients undergoing laparotomy. This is in contrast to a 32% pregnancy rate in patients who were managed expectantly.
Conclusions	No clear benefit of surgery could be documented, with an overall odds ratio of 1.24 (95% CI 0.50-2.98). This may be confounded by the selection of patients with less severe endometriosis for expectant management.

Authors and Year: D.S. Guzick and J.A. Rock (1983)

Title	"A Comparison of Danazol® and Conservative Surgery for the Treatment of Infertility due to Mild or Moderate Endometriosis."
Objective	To compare pregnancy following conservative surgery versus Danazol® in an infertile patient with mild or moderate endometriosis.
Design	A cohort study in which patients chose to receive either Danazol® therapy for 4-12 months or conservative surgical therapy.
Setting	Johns Hopkins Hospital, Baltimore, Maryland.
Patients	Two hundred and twenty-four infertile women with mild or moderate endometriosis, as documented by laparoscopy, underwent conservative surgery or received Danazol®. The duration of infertility was at least one year. Patients with other infertility factors were excluded.
Interventions	A total of 91 patients received Danazol® at a dose of between 400 and 800 mg/d for 4-12 months. One hundred and thirty-three patients underwent conservative laparotomy.
Major Outcomes Measured	Pregnancy.
Main Results	Seventy-six of 133 (57.1%) patients in the surgery group achieved pregnancy compared with 30/91 (33.0%) in the Danazol® group. This was, however, a function of follow-up duration. Cumulative pregnancy rates at 72 months were similar — 68.3% versus 74% following surgery and Danazol®, respectively.
Conclusions	The odds ratio for pregnancy of 2.71 (95% CI 1.50-4.80) suggests that surgery is a beneficial treatment when compared with Danazol® therapy for mild to moderate endometriosis. The limitations of this trial include the potential for bias secondary to a non-experimental design and the absence of a control group that received no therapy. Also, the difference in follow-up duration between groups is largely responsible for this apparent treatment effect.

Authors and Year: M.R. Henzl et al. (1988)

Title	"Administration of Nasal Nafarelin® as Compared with Oral Danazol® for Endometriosis: A Multicenter Double-Blind Comparative Clinical Trial."
Objective	This study was designed to assess Nafarelin®'s efficacy and to identify any adverse effects of treatment in a large patient population when compared with an active control (Danazol®).

Design	A double-blind randomized placebo-controlled trial with a six-month duration was performed. Follow-up was for 12 months post-treatment.
Setting	A multicentre North American trial with the principal investigator being located in Palo Alto, California.
Patients	Patients with laparoscopic- or laparotomy-diagnosed pelvic endometriosis were included in the study.
Interventions	Seventy-nine patients were allocated to treatment with 800 μg and 77 patients with 400 μg of Nafarelin® daily. This is in contrast to 80 patients who were randomized to treatment with 800 mg of Danazol® per day. The duration of therapy was 6 months, and follow-up was 12 months.
Main Outcomes Measured	Changes in the mean endometriosis score at laparoscopic evaluation; hormonal changes; pregnancy.
Main Results	All groups showed a decrease in laparoscopic endometriosis score; there was no significant difference between groups. Forty-two of 104 (40%) patients in the Nafarelin® group and 16/45 (36%) patients in the Danazol® group achieved pregnancy. Fewer side-effects were documented with Nafarelin®.
Conclusions	Nafarelin® has fewer side-effects than Danazol®. Both are effective in relieving pain associated with endometriosis. Nafarelin® did not result in improved conception post-treatment compared with Danazol®.

Authors and Year: M.E. Hull et al. (1987)

Title	"Comparison of Different Treatment Modalities of Endometriosis in Infertile Women."
Objective	To report on three modes of therapy for mild to moderate endometriosis associated with infertility.
Design	A descriptive triple-arm cohort study comparing the effects of medroxyprogesterone acetate, Danazol®, and expectant management in the treatment of endometriosis-related infertility. Treatment allocation was by physician and patient choice.
Setting	Wayne State University School of Medicine, Detroit, Michigan.
Patients	One hundred and forty-four patients with laparoscopically proven AFS Stage I or II endometriosis were described. Couples with any other infertility factor were excluded.
Interventions	Patients were selected for treatment with medroxyprogesterone acetate 10 mg TID for 90 d, Danazol® 600-800 mg/d for six months, or for no treatment. Patients were followed for a minimum of 18 months after therapy.

Main Outcomes Measured	Crude and cumulative pregnancy rates were calculated. Sixteen of 36 (44%) patients receiving medroxyprogesterone acetate conceived. This is in contrast to 18/52 (35%) patients receiving Danazol® and 21/56 (38%) patients managed expectantly. These differences did not reach statistical significance.
Conclusions	Neither of the treatment regimes described resulted in an improved pregnancy rate when compared with expectant management.

Author and Year: C.J. Levinson (1989)

Title	"Endometriosis Therapy: Rationale for Expectant or Minimal Therapy in Minimal/Mild Cases (AFSI)."
Objective	To compare the pregnancy rates of infertile patients with the diagnosis of mild endometriosis treated with Danazol® for six months, laparoscopic surgery alone, laparoscopic surgery with Danazol® therapy, or expectant management.
Design	A four-arm retrospective cohort study.
Setting	Children's Hospital of San Francisco, San Francisco, California.
Patients	One hundred and eighty-nine patients with AFS Stage I classification endometriosis with an indeterminate length of infertility were reviewed.
Interventions	Patients were treated by one of the four modalities described above. The dose of Danazol® is unspecified.
Main Outcomes Measured	Conception rate.
Main Results	At a follow-up period of 12 months, 9/21 (43%) of the patients managed expectantly conceived. This compared with 17/41 (41%) of patients treated with Danazol® alone, 44/83 (53%) of patients receiving laparoscopic surgery alone, and 23/44 (52%) of patients receiving laparoscopic surgery and post-operative Danazol® therapy. These results did not reach statistical significance.
Conclusions	Danazol®, laparoscopic surgery, or a combination of both are no more efficacious than expectant management.

Authors and Year: A.D. Noble and A.T. Letchworth (1979)

Title	"Medical Treatment of Endometriosis: A Comparative Trial."
Objective	To compare mestranol norethynodrel and Danazol® for the treatment of endometriosis.
Design	A randomized two-arm study (method of randomization not described) with six months of treatment for endometriosis.

Setting	Royal Hampshire County Hospital, Winchester, United Kingdom.
Patients	Patients with infertility or other symptoms in association with laparoscopically diagnosed and staged endometriosis were randomly allocated to receive one of two drugs.
Interventions	Mestranol norethynodrel 5 mg was given BID or Danazol® 100 mg BID. The dosage was increased every two weeks until the patient became amenorrhoeic. Treatments continued for a six-month period.
Main Outcomes Measured	An assessment was made of side-effects, improvements in laparoscopic score, improvements in symptoms other than infertility, and accrued pregnancy rate.
Main Results	The number of patients who became pregnant after a treatment session was 7/12 (58%) on Danazol® and 4/10 (40%) on mestranol norethynodrel. Danazol® demonstrated a slightly better rate of improving symptoms other than infertility when compared with mestranol norethynodrel.
Conclusions	The pregnancy rate was not statistically different between these two interventions. Danazol® appeared to improve symptoms other than infertility associated with endometriosis when compared with mestranol norethynodrel.

Authors and Year: K. Nowroozi et al. (1987)

Title	"The Importance of Laparoscopic Coagulation of Mild Endometriosis in Infertile Women."
Objective	To evaluate whether laparoscopic coagulation of endometriosis improves fertility.
Design	A two-arm quasi-randomized study (allocation by last digit of social security number) comparing laparoscopic fulguration of endometriotic implants versus diagnostic laparoscopy alone.
Setting	Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pennsylvania.
Patients	Patients presenting with laparoscopically diagnosed Stage I and II endometriosis were included. The minimum duration of infertility before surgery was 26 months. Those with "peritoneal implants" were excluded for fear of damage to the bowel, bladder, or vessels.
Interventions	1. Fulguration of all endometriotic implants on the surface of the peritoneum as well as fulguration of endometriomas measuring up to 10 mm in diameter using a unipolar microtip electrode. 2. No treatment other than diagnostic laparoscopy with retrograde chromoperturbation.

Main Outcomes Measured	Clinical pregnancy.
Main Results	Of the patients who underwent fulguration, 42/69 (60.9%) conceived within eight months of laparoscopy. Only 10/54 (18.5%) patients whose endometriotic implants were not coagulated achieved pregnancy ($p < 0.001$).
Conclusions	Laparoscopic fulguration of endometriotic implants appears to be beneficial in the treatment of endometriosis-associated infertility.

Authors and Year: D.L. Olive and K.L. Lee (1986)

Title	"Analysis of Sequential Treatment Protocols for Endometriosis-Associated Infertility."
Objective	To compare conservative surgical procedures and expectant management in the treatment of endometriosis-associated infertility.
Design	A two-arm prospective cohort study.
Setting	Duke University Medical Center, Durham, North Carolina.
Patients	One hundred and thirty consecutive patients with a diagnosis of infertility and endometriosis and no prior treatment were selected for the study. The duration of infertility is not reported.
Interventions	Patients were offered a choice between conservative surgical management and expectant management. Follow-up was for a total of 40 months.
Main Outcomes Measured	Pregnancy. Life-table analysis was performed to generate monthly fecundity rates.
Main Results	Thirty-seven of 88 (42%) patients treated by conservative surgical procedures conceived. This compared with 30/42 (71.4%) patients who were treated by expectant management alone. Thus, the pregnancy rate was significantly higher in those patients who formed the no-treatment arm of this study.
Conclusions	Conservative laparotomy does not appear to be effective in the treatment of endometriosis-related infertility when compared with expectant management alone.

Authors and Year: J.L. Pouly et al. (1987)

Title	"Laparoscopic Treatment of Endometriosis (Laser Excluded)."
Objective	To report on the results of laparoscopic ablation of endometriotic implants with and without the adjuvant use of Danazol® in the infertility-directed treatment of endometriosis.

Design	A four-arm retrospective cohort study consisting of a comparison between laparoscopic ablation and no laparoscopic ablation with or without the use of Danazol®. Treatment allocation was by physician choice.
Setting	Polyclinique de Gynécologie obstétrique et Reproduction, Clermont-Ferrand, France.
Patients	Fifty-two patients presenting for infertility treatment who were found to have endometriosis that could not be treated using conventional laparoscopy were included. Duration of infertility was > 2 years. Mean AFS score in the laparoscopic surgery group was 9.6 versus 4.4 in the no-surgery patients ($p < 0.0001$).
Interventions	Patients received laparoscopic surgery alone, laparoscopic surgery with Danazol® treatment, no laparoscopic surgery, or Danazol® alone. The Danazol® regimen is not reported. However, the treatment duration was six months. Follow-up was for 14-37 months.
Main Outcomes Measured	Pregnancy.
Main Results	Nineteen of 29 (65.5%) patients treated with a combination of Danazol® and laparoscopy conceived. This compared with 4/6 (66.7%) patients treated with laparoscopic ablation alone. In those patients who did not receive laparoscopic treatment, 4/10 (40.0%) conceived with Danazol® compared with 3/7 (42.9%) who conceived with no treatment.
Conclusions	Patients with more severe disease were more likely to be exposed to laparoscopic surgery. Danazol®, laparoscopic surgery, or both did not improve the conception rate when compared with no treatment.

Authors and Year: L. Ronnberg and P.A. Jarvinen (1984)

Title	"Pregnancy Rates Following Various Therapy Modes for Endometriosis in Infertile Patients."
Objective	The purpose of this study was to compare pregnancy rates after conservative surgery with or without post-operative Danazol® treatment, Danazol® therapy alone, and laparoscopic electrocautery of endometriotic foci with post-operative Danazol® in infertile patients.
Design	A retrospective cohort study with four treatment arms.
Setting	University of Oulu, Oulu, Finland.
Patients	Patients complaining of infertility with a laparoscopic diagnosis of endometriosis who underwent one of the treatments under study over a five-year period were reviewed. Mean age ranged from 26 years in the untreated group (n = 4) to 30 years in the

	surgery and Danazol® group. Patients treated with conservative laparotomy and adjuvant Danazol® had a higher endometriosis score (AFS) than those in the other groups.
Interventions	1. Conservative laparotomy alone. 2. Laparotomy with Danazol® 600 mg daily over a six-month period. 3. Laparoscopic electrocautery of endometriotic foci followed by Danazol®. 4. Danazol® alone. 5. No treatment.
Main Outcomes Measured	Clinical pregnancy.
Main Results	The conception rate of patients undergoing conservative laparotomy only was 43% (39/90). Of those patients who were treated with conservative surgery with adjuvant Danazol®, 14/44 (32%) achieved pregnancy. This compared with 33/59 (56%) patients who were treated with Danazol® alone and 3/18 (17%) who were treated with laparoscopic electrocauterization alone.
Conclusions	No treatment modality in particular resulted in a significantly increased pregnancy rate in these patients. Important differences exist between treatment groups.

Authors and Year: R.S. Schenken and L.R. Malinak (1982)

Title	"Conservative Surgery Versus Expectant Management for the Infertile Patient with Mild Endometriosis."
Objective	To evaluate the need to treat patients with mild endometriosis by comparing conservative surgery and expectant management.
Design	A retrospective two-arm cohort study comprising patients with laparoscopically identified endometriosis who were treated with either conservative laparotomy or observation.
Setting	Department of Obstetrics and Gynecology, University of Texas Health Science Center at San Antonio, Texas.
Patients	Ninety patients accrued over an eight-year period with mild endometriosis were included in the cohort. Forty-five had endometriosis alone, and 45 also had an ovulatory factor or male infertility.
Interventions	In a non-randomized fashion, patients were allocated to receive either diagnostic laparoscopy or conservative surgery.
Main Outcomes Measured	Clinical pregnancy.
Main Results	Considering those patients with endometriosis alone, 12/16 (75.0%) managed expectantly achieved pregnancy compared

	with 21/29 (72.4%) of those who underwent conservative laparotomy.
Conclusions	There was no obvious benefit to performing conservative surgery versus expectant management in patients with mild endometriosis.

Authors and Year: J.C. Seiler, G. Gidwani, and L. Ballard (1986)

Title	"Laparoscopic Cauterization of Endometriosis for Fertility: A Controlled Study."
Objective	The purpose of the study was to compare electrocoagulation through laparoscopy with Danazol® therapy in the treatment of endometriosis-associated infertility.
Design	A two-arm prospective cohort study allocation to either laparoscopic electrocoagulation or six months of Danazol® therapy.
Setting	Cleveland Clinic, Cleveland, Ohio.
Patients	Ninety consecutive patients with laparoscopic diagnosis of moderate endometriosis with concomitant infertility were treated as described above.
Interventions	Patients received either electrocautery + lysis of adhesions through the laparoscope or six months of Danazol® therapy (dose not reported).
Main Outcomes Measured	Pregnancy.
Main Results	Four patients discontinued Danazol® therapy within three weeks of treatment. Conception occurred in 16/41 (39%) patients who completed the six months of Danazol® therapy. This compared with 20/45 (44%) of those patients treated with laparoscopic cauterization.
Conclusions	The authors were unable to demonstrate a clear benefit of either Danazol® therapy or laparoscopic cauterization in the infertility-directed treatment of endometriosis.

Author and Year: S. Telimaa (1988)

Title	"Danazol® and Medroxyprogesterone Acetate Inefficacious in the Treatment of Infertility in Endometriosis."
Objective	To compare the efficacy of Danazol® and medroxyprogesterone acetate compared with placebo in the treatment of infertility in patients with endometriosis.
Design	A triple-arm randomized trial (method of randomization not described) included groups treated with Danazol®, medroxyprogesterone acetate, and placebo.

Setting	University of Oulu, Oulu, Finland.
Patients	Forty-nine patients presenting with infertility and suffering from laparoscopically diagnosed endometriosis were included. In addition to one of the treatment arms, patients underwent laparoscopy with electrocautery or conservative laparotomy with excision of endometrial implants. The mean duration of infertility was 4.1-4.2 years. Mean female age ranged from 27.8 to 29.4 years.
Interventions	Patients were allocated by unknown means to one of three treatment groups. These included Danazol® 600 mg/d, medroxyprogesterone acetate 100 mg/d, or placebo for a total of six months.
Main Outcomes Measured	Clinical pregnancy.
Main Results	Six patients in the Danazol® group (33%), seven patients in the medroxyprogesterone acetate group (42%), and six patients in the placebo group (46%) conceived.
Conclusions	There was no significant difference between the pregnancy rates in the three groups. Time-series analysis demonstrated delayed fecundation in patients undergoing ovarian suppressive therapy.

Authors and Year: E.J. Thomas and I.D. Cooke (1987)

Title	"Successful Treatment of Asymptomatic Endometriosis: Does It Benefit Infertile Women?"
Objective	To address the question of whether endometriosis is a causal agent of infertility by comparing gestrinone and placebo in the infertility-directed treatment of endometriosis.
Design	A two-arm randomized double-blind study (method of randomization not described) with 24 weeks of treatment and 12 months of follow-up.
Setting	The Jessop Hospital for Women, Sheffield, United Kingdom.
Patients	Patients complaining of at least 12 months of primary or secondary infertility with a laparoscopic diagnosis of endometriosis were included. Those with tubal involvement were excluded. Median age, duration of infertility, parity, and body mass index were similar between groups.
Interventions	Patients were randomized to receive placebo or gestrinone 2.5 mg twice weekly for a total of 24 weeks.
Main Outcomes Measured	Clinical pregnancy.
Main Results	Of those patients treated with gestrinone, 5/20 (25%) conceived within 12 months. This is compared with 4/17 (24%) in the placebo group.

Conclusions	Gestrinone did not appear to be beneficial when compared with placebo in the infertility-directed treatment of endometriosis.

Appendix 3. Structured Abstracts — Controlled Trials in Assisted Reproductive Technology

Authors and Year: H.I. Abdalla et al. (1990)

Title	"Comparative Trial of Luteinizing Hormone-Releasing Hormone Analog/Human Menopausal Gonadotropin and Clomiphene Citrate/Human Menopausal Gonadotropin in an Assisted Conception Program."
Objective	Does the use of buserelin acetate in a flare-up regime improve clinical outcomes of IVF when compared with clomiphene/hMG?
Design	This was a two-arm study with quasi-random treatment allocation by alternating days of consultation visits. There was no stratification for diagnostic group or IVF versus GIFT treatment.
Setting	IVF Unit, Cromwell and Middlesex Hospitals, London, United Kingdom.
Patients	It appears that all patients presenting for IVF or GIFT were allocated to treatment groups. Mean female age was 33-33.5 years.
Interventions	Between April 1986 and June 1987, 220 cycles in 174 patients were "randomized" between: 1. clomiphene (100 mg days 2-6) and hMG titrated to response; 2. buserelin 100 μg five times daily by nasal spray with hMG titrated to response. The buserelin was started on day 1 of the treatment cycle in conjunction with hMG. All patients received luteal support with hCG 2 000 units days 2, 5, and 8 following retrieval.
Main Outcomes Measured	Clinical pregnancy; spontaneous abortion; live birth.
Main Results	When GIFT and IVF data were combined, a significant increase in clinical pregnancy rate was noted in the Gn-RHa/hMG group (30.6% versus 16.1%, $p < 0.02$). When data were separated into IVF and GIFT treatments, statistical significance was absent. The rate of spontaneous abortion based upon combined IVF and GIFT data was also significantly increased in the clomiphene/hMG group (35.7% versus 9.1%, $p < 0.05$).

	Live birth rate was significantly higher in the Gn-RHa/hMG group than in the CC/hMG group (21 versus 8%, $p < 0.01$).
Conclusions	The increased pregnancy rate in the combined IVF and GIFT patients associated with Gn-RHa use may be related to a larger number of oocytes collected and embryos formed. It may also be related to the asymmetry of treatment allocation — 64% of GIFT cycles received Gn-RHa. This was not a factor pointed out by the authors.

Authors and Year: J.M. Antoine et al. (1990)

Title	"Ovarian Stimulation Using Human Menopausal Gonadotrophins With or Without LHRH Analogues in a Long Protocol for In-Vitro Fertilization: A Prospective Randomized Comparison."
Objective	To determine the efficacy of a Gn-RHa ovulation induction protocol versus hMG alone in normovulatory patients undergoing IVF.
Design	Two-arm study, randomized by sealed envelope.*
Setting	Hôpitals Tenon and Necker, Paris, France.
Patients	One hundred and eight women 38 years of age or less undergoing IVF for tubal factor infertility (male factor excluded).
Interventions	1. Decapeptyl 3.75 mg IM commenced at any stage during the preceding cycle. hMG began 28 d later (n = 90). 2. hMG alone beginning day 2 of the treatment cycle (n = 90).
Main Outcomes Measured	Cycles cancelled; number of oocytes; clinical pregnancy; spontaneous abortion.
Main Results	Cycle cancellation was twice as common in the hMG alone group (26 versus 13 cycles, $p < 0.02$). Clinical pregnancy rate per cycle commenced was 11/90 versus 19/90 (non-significant) in the hMG and Gn-RHa groups, respectively. The mean number of embryos frozen did not differ significantly between groups. Ovarian hyperstimulation occurred in three patients of the Gn-RHa group, but none of the hMG-alone patients.
Conclusions	Advantages of Gn-RHa include decreased cycle cancellation and increased total oocyte and embryo numbers. The trend toward increased ongoing pregnancy rates with Gn-RHa use was not confirmed by these data.

* Information obtained from author.

Authors and Year: J. Belaisch-Allart et al. (1987)

Title	"The Effect of Dydrogesterone Supplementation in an IVF Programme."
Objective	To determine the efficacy of dydrogesterone luteal phase support versus placebo following IVF-ET.
Design	This was a two-arm randomized double-blind trial. A "double-blind randomized list" was used for treatment allocation.
Setting	Hôpital Béclère, Clamart, France.
Patients	Two hundred and eighty-six consecutive IVF patients were included from September 1985 to February 1986. Patients were randomized on day of retrieval if one or more oocytes were obtained.
Interventions	Dydrogesterone 10 mg TID PO beginning on the evening of oocyte retrieval versus one placebo tablet TID over same time period.
Main Outcomes Measured	Serum progesterone, days 3, 6, and 9; clinical pregnancy.
Main Results	Estrogen and progesterone levels were similar between groups. Twenty-seven of 141 cycles following dydrogesterone resulted in pregnancy, of which seven aborted. Twenty out of 145 in the placebo group conceived, with four abortions. Ongoing pregnancy rates, therefore, were 16% and 12%, respectively (non-significant).
Conclusions	No significant difference was noted between dydrogesterone and placebo in terms of pregnancy. However, this study had insufficient power to detect clinically significant differences at the level that might have been expected.

Authors and Year: J. Buvat et al. (1988)

Title	"A Randomized Trial of Human Chorionic Gonadotropin Support Following In Vitro Fertilization and Embryo Transfer."
Objective	To assess the efficacy of hCG versus no treatment in the luteal phase following IVF-ET.
Design	Quasi-randomization based on the date of oocyte retrieval.
Setting	Association EPARP, Lille, France.
Patients	One hundred and sixteen consecutive cycles with ET. This suggests that cases randomized on the day of retrieval were not all included.
Interventions	hCG 1 500 IU IM days 2, 4, and 6 post-retrieval versus no luteal support.
Main Outcomes Measured	Clinical pregnancy.

Main Results	There was no significant difference in the clinical pregnancy rate with or without hCG support. Implantation rates were 13.9% and 10.4%, respectively. The spontaneous abortion rate was not reported.
Conclusions	The only difference between treatment groups was a significant increase in the duration of the luteal phase with the lowering of the estradiol:progesterone ratio in association with hCG use.

Authors and Year: J. Buvat et al. (1990)

Title	"Luteal Support After Luteinizing Hormone-Releasing Hormone Agonist for In Vitro Fertilization: Superiority of Human Chorionic Gonadotropin over Oral Progesterone."
Objective	To determine the efficacy of hCG versus oral progesterone following IVF with ovulation induction using a Gn-RHa protocol.
Design	Quasi-randomized two-arm trial with sequential allocation at the time of retrieval. Note: Only data on cycles with transfer are reported (failed fertilization cycles ignored).
Setting	Association EPARP, Lille, France.
Patients	Included were all women undergoing IVF with Gn-RHa ovulation induction over a 10-month period in whom at least one embryo was produced.
Interventions	hCG 1 500 IU on days 0, 2, and 4 post-oocyte retrieval versus micronized progesterone 400 mg daily PO from 1 d post-retrieval to menses.
Main Outcomes Measured	Implantation rate; clinical pregnancy; ongoing pregnancy.
Main Results	Clinical pregnancy occurred following 22/70 hCG cycles and 10/70 progesterone cycles ($p < 0.05$). Twenty-one and eight, respectively, of these were ongoing ($p < 0.01$). hCG-treated cycles had longer luteal phases, 12.9 versus 12.1 ($p < 0.05$). Moderate hyperstimulation was observed in two cases in the hCG group and none in the randomized progesterone group.
Conclusions	Adequate luteal support significantly improves the results of IVF following Gn-RHa. hCG is superior to oral progesterone. OHSS was no more common in hCG-supported patients than in concurrent non-hCG-supported patients.

Authors and Year: M. Dirnfeld et al. (1991)

Title	"A Randomized Prospective Study on the Effect of Short and Long Buserelin Treatment in Women with Repeated

	Unsuccessful In Vitro Fertilization (IVF) Cycles due to Inadequate Ovarian Response."
Objective	To compare two modes of Gn-RHa treatment (flare-up versus suppression protocols) in IVF patients showing previous poor response to ovarian stimulation.
Design	Two-arm randomized trial with data from previous poor stimulation cycles. Randomization was by "random number table."
Setting	Carmel Hospital, Haifa, Israel.
Patients	Fifty-four women were included with one or two previous poor responses to ovulation induction for IVF.
Interventions	1. Suppression with 1 000 µg/d buserelin beginning 15-30 d pre-stimulation with hMG. 2. Flare-up with 600 µg/d buserelin beginning day 1 of treatment along with hMG.
Main Outcomes Measured	Cycle cancellation; oocytes retrieved; clinical pregnancy.
Main Results	Both approaches gave improved results compared with previous stimulation. The long protocol resulted in fewer cycle cancellations (2:10, $p < 0.01$), more oocytes (7.0:5.6, $p > 0.01$), and more clinical pregnancies (8:2, $p < 0.05$). However, more ampoules of hMG were required (22:16, $p < 0.05$).
Conclusions	Gn-RHa suppression in previous poor responders appears to improve IVF outcome to a greater extent than flare-up administration.

Authors and Year: A. Ferrier et al. (1990)

Title	"Evaluation of Leuprolide Acetate and Gonadotropins Versus Clomiphene Citrate and Gonadotropins for In Vitro Fertilization or Gamete Intrafallopian Transfer."
Objective	To compare the "efficiency" of two ovarian stimulation protocols for IVF or GIFT: CC/hMG versus leuprolide + hMG.
Design	Two-arm study assigning consecutive new patients to one of two protocols. Method of randomization was not described.
Setting	Cornell University Medical Center, New York.
Patients	New patients less than 45 years of age undergoing IVF or GIFT. Major asymmetry exists between groups. Among the CC/hMG patients, there were none with tubal factor, endometriosis, or unexplained infertility, but there were 83% with male factor. The leuprolide group only had 18% male factor.
Interventions	1. CC/hMG from cycle day 3.

2. Leuprolide 0.1 mg SC daily from cycle day 1, with hMG commencing on cycle day 3.
3. Different luteal support protocols were used for each group.

Main Outcomes Measured: Clinical pregnancy; multiple pregnancy; spontaneous abortion.

Main Results: Despite the asymmetry between groups, clinical pregnancy occurred as follows:

	Gn-RHa/hMG	CC/hMG
IVF	1/23	6/32
GIFT	2/6	2/9

Conclusions: No significant difference was noted between these protocols.

Authors and Year: Y. Gonen et al. (1991)

Title: "The Use of Long-Acting Gonadotropin-Releasing Hormone Agonist (GnRH-a; Decapeptyl) and Gonadotropins Versus Short-Acting GnRH-a (buserelin) and Gonadotropins Before and During Ovarian Stimulation for In Vitro Fertilization (IVF)."

Objective: To determine the efficacy of depot suppression and short-acting suppression with two different Gn-RHa versus standard ovulation induction with hMG alone in IVF patients.

Design: This was a quasi-random three-arm study with allocation according to "expected date of menses." If this occurred on Wednesday, Thursday, or Friday, women received hMG alone. If it occurred on other days, patients alternated between Gn-RHa protocols.

Setting: Carmel Medical Centre, Haifa, Israel.

Patients: Consecutive IVF patients were included. Mean female age was 32 years. Significantly more patients with tubal factor infertility entered the decapeptyl group.

Interventions:
1. Decapeptyl depot IM, 3.2 mg, on day 3 of the preceding cycle. hMG three ampoules daily beginning 24 days later (n = 54).
2. Buserelin 1 200 mg IN on day 21 of preceding cycle for 10 days. Dosage then reduced to 600 µg daily and three ampoules hMG given daily also (n = 66).
3. hMG three ampoules daily from day 3 of the treatment cycle (n = 55).

Main Outcomes Measured	Number of oocytes; dose of hMG; clinical pregnancy; spontaneous abortion.
Main Results	More hMG was used in the Gn-RHa treated groups than in the group receiving hMG alone. Cancellation rates are not given as oocyte retrieval is the denominator. Clinical pregnancy rates were 19/70 for buserelin/hMG, 7/57 for decapeptyl/hMG, and 10/59 for hMG alone. Comparison of decapeptyl/hMG with buserelin/hMG reached statistical significance ($p < 0.05$), but when compared with hMG alone, no significant difference was noted. Spontaneous abortion was also more common in the decapeptyl/hMG group (5/7) compared with the buserelin/hMG group (5/19, $p < 0.05$). The abortion rate with hMG alone was 4/10 (non-significant).
Conclusions	Buserelin/hMG is superior to decapeptyl/hMG in terms of the ongoing pregnancy rate. Neither regime was significantly different from routine hMG alone.

Authors and Year: A. Herman et al. (1990)

Title	"Pregnancy Rate and Ovarian Hyperstimulation After Luteal Human Chorionic Gonadotropin in In Vitro Fertilization Stimulated with Gonadotropin-Releasing Hormone Analog and Menotropins."
Objective	To assess the pregnancy rate and frequency of OHSS after luteal phase hCG administration in IVF-ET cycles using Gn-RHa/hMG/hCG for ovulation induction.
Design	On the day of transfer, patients were randomized "sequentially" to either hCG or no treatment (quasi-randomized two-arm study).
Setting	Tel Aviv University Medical School, Tel Aviv, Israel.
Patients	Thirty-six consecutive IVF patients undergoing ET. Demographic data were not given, but groups were described as "similar."
Interventions	hCG 2 500 IU IM days 0, 2, 5, and 8 post-transfer. Control group received no treatment.
Main Outcomes Measured	Clinical pregnancy; OHSS.
Main Results	Clinical pregnancy occurred following 9/18 transfers with hCG and 3/18 without hCG. Five cases of moderate to severe OHSS were noted, all following hCG support.
Conclusions	The clinical pregnancy rate is enhanced, but the risk of OHSS is increased, with hCG luteal phase support.

Authors and Year: C.J. Kubik et al. (1990)

Title	"Randomized, Prospective Trial of Leuprolide Acetate and Conventional Superovulation in First Cycles of In Vitro Fertilization and Gamete Intrafallopian Transfer."
Objective	To compare clinical outcomes following CC and hMG versus SC Lupron® suppressive treatment + hMG for ovulation induction prior to IVF or GIFT.
Design	Treatment allocation at the time of cycle scheduling was quasi-random by alternating patient. Of 132 eligible patients randomized, 114 went on to treatment.
Setting	Magee-Women's Hospital, Pittsburg, Pennsylvania, 1988-1989.
Patients	One hundred and seventy-three patients undergoing IVF-ET or GIFT were evaluated in first cycle, with no prior poor response to ovarian stimulation (presumably all were previously treated with hMG). Of the 132 patients randomized, 18 cancelled before undergoing treatment (self-selection).
Interventions	Protocol 1: Clomiphene 100 mg days 5-9 plus hMG three ampoules beginning on day 9 (n = 54). Protocol 2: Lupron® 50-100 µg daily SC days 21-24 of luteal phase, with suppression of LH < 15 before starting hMG three ampoules (n = 60). Additional hMG was tailored according to response. hCG was given when three follicles reached 17-23 mm and estradiol concentrations were > 800 pg/mL.
Main Outcomes Measured	Oocytes retrieved and fertilized; embryos transferred; clinical pregnancy rate; endocrine response. Pregnancy was defined as a gestation in which serum ßhCG was greater than 250 IU. Some chemical pregnancies, therefore, were included.
Main Results	More patients cancelled prior to clomiphene hMG than prior to Lupron®. Proportions of patients undergoing GIFT and IVF were similar in each group. Significantly more patients reached retrieval with protocol 2 (87% versus 61%). The pregnancy rate per retrieval was not significantly different (39% versus 44%) in groups one and two, respectively. However, male factor was more common in group two. With Lupron®, likelihood of retrieval was 1.4:1 when compared with CC/hMG. The total number of oocytes increased, but the number of mature oocytes was similar between the two groups. Ongoing pregnancy data are as follows:

	Protocol 1 (CC/hMG)	Protocol 2 (Gn-RHa/hMG)
IVF	7.7%	17.6%
GIFT	21.4%	42.3%

These differences are not statistically significant.

Conclusions — Gn-RHa use for routine ovulation induction is justifiable on the basis of decreased cycle cancellation and potentially better ongoing pregnancy rates.

Authors and Year: M.J. Kupferminc et al. (1990)

Title — "A Prospective Randomized Trial of Human Chorionic Gonadotrophin or Dydrogesterone Support Following In-Vitro Fertilization and Embryo Transfer."

Objective — To determine the efficacy of luteal phase support with hCG or progesterone following IVF-ET.

Design — Three-arm randomized controlled study.

Setting — Serline Maternity Hospital, Tel Aviv Medical Centre, Tel Aviv, Israel.

Patients — One hundred and fifty-six patients undergoing IVF-ET were included between March 1988 and April 1989. Mean female age ranged from 32.5 to 33.6 years. Diagnostic categories were evenly distributed between treatment groups.

Interventions — Fifty-four patients received dydrogesterone (duphaston) 10 mg PO TID beginning on the day of embryo transfer; 51 received hCG 2 500 units IM days 3, 6, and 10 post-embryo transfer; and 51 received placebo PO TID. Both dydrogesterone and placebo groups received medication for 14 d.

Main Outcomes Measured — Serum progesterone; duration of luteal phase; clinical pregnancy; chemical pregnancy; clinical abortion; ongoing pregnancy.

Main Results — Clinical pregnancy rates were similar in the three treatment groups: progesterone 29.6%, hCG 23.5%, placebo 27.4%. Chemical and clinical abortion rates were also similar.

Conclusions — Although the luteal phase was longer with hCG, no significant benefit was demonstrated through progesterone or hCG supplementation in terms of clinical pregnancy or spontaneous abortion rates.

Authors and Year: J. Leeton, A. Trounson, and D. Jessup (1985)

Title	"Support of the Luteal Phase in In Vitro Fertilization Programs: Results of a Controlled Trial with Intramuscular Proluton®."
Objective	To determine whether extension of the luteal phase with exogenous progesterone would have a positive effect on the establishment of IVF pregnancies.
Design	Two-arm quasi-random study with alternating patient allocation to Proluton® IM versus no treatment.
Setting	Monash University/Epworth In Vitro Fertilization Centre, Epworth Medical Centre, Melbourne, Victoria, Australia.
Patients	One hundred and eighty-six consecutive IVF patients were included from May 1983 to April 1984. Thirty-four women had suspected luteal phase defects.
Interventions	Progesterone in oil (Proluton®) 50 mg IM daily days 7-16 post-oocyte retrieval versus no treatment. All patients received a combination of CC/hMG for ovulation induction.
Main Outcomes Measured	Clinical and ongoing pregnancy.
Main Results	Pregnancy occurred in 14/72 cycles with progesterone and 12/80 with no luteal support. Two miscarriages occurred in the former and three in the latter group. Ten of 34 women treated with progesterone in a non-random fashion conceived. There were no significant differences between groups.
Conclusions	Routine administration of progesterone luteal phase support does not appear to enhance ongoing clinical pregnancy.

Authors and Year: E. Loumaye et al. (1989)

Title	"Hormonal Changes Induced by Short-Term Administration of a Gonadotropin-Releasing Hormone Agonist During Ovarian Hyperstimulation for In Vitro Fertilization and Their Consequences for Embryo Development."
Objective	To determine the differences between flare-up and suppression Gn-RHa regimes in terms of hormonal parameters monitored during the follicular phase.
Design	Randomized controlled trial (method of allocation not described).
Setting	Physiology of Human Reproduction Unit, Department of Obstetrics and Gynaecology, University of Louvain, Brussels, Belgium.
Patients	Included were 18 consecutive patients less than 40 years of age with tubal factor infertility and both ovaries present. A

separate non-random control group of 13 spontaneously menstruating women was also included.

Interventions

1. Group A patients (n = 9) received buserelin 900 µg daily from day 1 of menses.
2. Group B (n = 9) received 900 µg buserelin IN from day 21 of the previous menstrual cycle.

Both groups began hMG 225 IU from day 3 of menstruation.

Main Outcomes Measured

Endocrine response; clinical pregnancy.

Main Results

Serum LH concentrations in group A were significantly elevated from days 2 to 8 of the follicular phase compared with normal cycling controls and group B's Gn-RHa patients. Serum FSH levels were high in group A on day 2 of the cycle, then dropping on day 3 and stabilizing well above control values. In group B, FSH was in the upper normal range on days 2 and 3 and then rose when hMG commenced. Estradiol levels rose sooner in group B and remained higher throughout the remainder of the follicular phase. Progesterone was elevated in group A for the first five days of treatment, dropping on day 6. Similar numbers of oocytes were obtained. More high-quality embryos were obtained from the suppressed patient group than the flare-up patient group. Two ongoing pregnancies were obtained in the suppressed group and only one spontaneous abortion in the flare-up group.

Conclusions

Flare-up administration of buserelin resulted in an increase in the plateau of LH for four to five days. This was associated with a significant progesterone increase. Both regimes prevented spontaneous LH surge. Follicular recruitment does not appear to be different between the two groups, but the oocyte fertilization rate and number of high-quality embryos were significantly reduced in the flare-up patients.

Authors and Year: J.C. McBain et al. (1987)

Title

"A Randomized Trial of Progesterone Support Following Ovarian Stimulation with Clomiphene hMG for IVF and GIFT."

Objective

To assess the efficacy of progesterone pessaries in supporting the luteal phase of IVF and GIFT patients.

Design

Quasi-random allocation by alternating patient. GIFT and IVF data were stratified and reported separately.

Setting

Royal Women's Hospital, Melbourne, Australia.

Patients

Consecutive IVF and GIFT patients. Demographics were not described.

Interventions	Progesterone 50 mg by pessary for 14 d, beginning on the day of ET or 3 d post-GIFT, compared with no treatment.
Main Outcomes Measured	Clinical pregnancy.
Main Results	No significant differences in clinical pregnancy rate were noted among the four groups — range 23.2-25.6%.
Conclusions	Progesterone should not routinely be given in the luteal phase following IVF or GIFT.

Authors and Year: G.B. Maroulis et al. (1991)

Title	"Prospective Randomized Study of Human Menotropin Versus a Follicular and a Luteal Phase Gonadotropin-Releasing Hormone Analog-Human Menotropin Stimulation Protocols for In Vitro Fertilization."
Objective	To compare clinical outcomes of IVF following ovulation induction using Gn-RHa beginning in the luteal or follicular phase versus an hMG/FSH protocol.
Design	Three-arm quasi-randomized study. Patients were allocated to treatment arms according to the order in which they called the coordinator. There was a significant discrepancy between group sizes due to a change in randomization protocol during the trial: 93 in group A, the hMG/FSH protocol; 64 in group B with Gn-RHa suppression; and 35 in group C, the Gn-RHa flare-up protocol.
Setting	University of Florida, College of Medicine and Human Women's Hospital, Tampa, Florida.
Patients	One hundred and ninety-two women suffering from various forms of intractable infertility were included. There was no age limit. Distribution of tubal factor, endometriosis, male factor, unexplained infertility, and ovulatory dysfunction was similar between treatments. Approximately 70% of all patients had tubal factor infertility. All patients underwent a single cycle of treatment.*
Interventions	Ovulation induction for IVF using hMG/FSH, Gn-RHa suppression with leuprolide acetate 1 mg/d for 10-14 d pre-treatment or Gn-RHa flare-up using 0.75-1 mg leuprolide acetate from cycle day 2.
Main Outcomes Measured	Cycle cancellation; implantation; clinical pregnancy.
Main Results	Cycle cancellation was significantly more frequent in the hMG/FSH versus Gn-RHa groups (32% versus 11% and 14%).

* Information obtained from author.

	There was no significant difference in the clinical pregnancy rate per cycle initiated (15%, 14%, and 15%). Implantation rates were 9.3, 6.9, and 7.3 for groups A, B, and C, respectively. Total numbers of oocytes retrieved and embryos resulting were significantly higher in groups B and C using Gn-RHa.
Conclusions	Although Gn-RHa did not significantly improve the clinical pregnancy rate per treatment cycle initiated, it did effectively reduce the cycle cancellation rate and resulted in more embryos for freezing than the hMG/FSH protocol. Note: The spontaneous abortion rate was not reported.

Authors and Year: S. Nader et al. (1988)

Title	"Luteal-Phase Support in Stimulated Cycles in an In Vitro Fertilization/Embryo Transfer Program: Progesterone Versus Human Chorionic Gonadotropin."
Objective	To compare serum estradiol (E) and progesterone (P) concentrations following IVF-ET with either hCG or progesterone in oil luteal phase support.
Design	Two-arm randomized study (method of allocation not described) with 17 patients undergoing 20 cycles. Whether randomization was at cycle onset or ET was not stated.
Setting	University of Texas Health Science Center.
Patients	IVF patients, no information on demographics or whether consecutive.
Interventions	Ovulation induction was with clomiphene/hMG in 18 cycles and hMG alone in two cycles. This was followed by 25 mg P in oil IM daily from days 4 to 18 post-transfer versus hCG 1 500 IU on days 4, 7, 10, or 13.
Main Outcomes Measured	Serum E; P; ßhCG; clinical pregnancy.
Main Results	Including the three clinical pregnancies (but excluding one biochemical pregnancy), serum P was higher in the hCG group. This may reflect a greater number of follicles observed by chance in that group. In the P-treated group, the luteal P:luteal E ratio was higher because of the lower luteal E achieved. Three clinical pregnancies occurred following hCG and none following P.
Conclusions	The absence of pregnancies in the P group suggests that a high P:E ratio in the luteal phase is not necessary for conception.

Authors and Year: S. Neveu et al. (1987)

Title	"Ovarian Stimulation by a Combination of a Gonadotropin-Releasing Hormone Agonist and Gonadotropins for In Vitro Fertilization."
Objective	To evaluate the use of Gn-RHa (buserelin) in ovarian stimulation for IVF.
Design	Two-arm randomized trial, method of allocation not described.
Setting	Université de Montpellier, Montpellier, France.
Patients	Twenty women aged 28-38 years with tubal infertility were included. Endocrine abnormality, male factor, and unexplained infertility were excluded.
Interventions	1. FSH 225 units daily from day 2. 2. Buserelin 0.3 mL SC BID beginning on days 1-2 of the previous cycle. When suppression was confirmed, gonadotropin administration began. Ten patients with previous poor stimulation were also assessed. All received hCG luteal support.
Main Outcomes Measured	Cycle cancellation; oocyte number; fertilization rate; clinical and multiple pregnancy.
Main Results	More oocytes were obtained following Gn-RHa suppression (8.2 versus 4.8, $p < 0.05$). Six clinical pregnancies were obtained with Gn-RHa treatment and one with FSH alone. Three of the buserelin pregnancies were multiple. In the previously poor responders receiving buserelin, four pregnancies occurred.
Conclusions	Buserelin pre-treatment may improve the clinical pregnancy rate in both normal and poor responders, though the level of statistical significance for clinical pregnancy data was not reported.

Authors and Year: D.W. Polson et al. (1991)

Title	"A Controlled Study of Gonadotropin-Releasing Hormone Agonist (Buserelin Acetate) for Folliculogenesis in Routine In Vitro Fertilization Patients."
Objective	Does IN buserelin (given in one of two doses) improve the outcome of IVF patients when compared with hMG alone?
Design	Randomized controlled trial. Method of randomization described as "central."
Setting	Monash University/Epworth Medical Centre, IVF Units, Melbourne, Australia.
Patients	One hundred and fifty-seven women with either tubal or idiopathic infertility who had previously undergone successful

	stimulation with CC-hMG were randomized to receive either hMG alone or hMG in combination with buserelin acetate 600 μg/d or 1 200 μg/d.
Interventions	Fifty women received hMG alone, 51 received buserelin acetate 600 μg/d, and 56 received buserelin acetate 1 200 μg/d. Buserelin acetate was administered until the patient was suppressed (as defined by estrogen levels of less than 180 pmol/L on two consecutive days) prior to starting hMG. In hMG-alone cycles, treatment started on day 3. Standard regimes of hMG administration were used based on the patient's response.
Main Outcomes Measured	Clinical pregnancy; hMG dose; cycle cancellation.
Main Results	Similar lengths of time were needed for suppression regardless of the dose of buserelin used. In the stimulation phase, cycles using hMG alone were more likely to be abandoned, primarily because of LH surges. Only 7 of 120 buserelin cycles were cancelled, usually because of poor follicular development. Patients on 600 μg buserelin took less time to stimulate and required less hMG per cycle compared with patients on 1 200 μg buserelin. Similar numbers of follicles were obtained regardless of the stimulation protocol used. Fertilization rates were also similar. The peak serum estradiol level prior to hCG administration was significantly lower in both of the buserelin groups than in the hMG-alone group. Similar clinical pregnancy rates were obtained per ET for the three groups.
Conclusions	Although Gn-RHa are effective in reducing the number of cycles cancelled due to LH surge, there is no clear evidence for improved folliculogenesis. The pregnancy rate per ET was similar for all groups. The buserelin groups required a significantly longer stimulation period as well as increased hMG requirements. There was no support for using 1 200 μg of buserelin rather than 600 μg.

Authors and Year: V. Remorgida et al. (1989)

Title	"The Duration of Pituitary Suppression by Means of Intranasal Gonadotropin Hormone-Releasing Hormone Analogue Administration Does Not Influence the Ovarian Response to Gonadotropin Stimulation and Success Rate in a Gamete Intrafallopian Transfer (GIFT) Program."
Objective	To compare the efficacy of flare-up versus suppression Gn-RHa protocols in women undergoing their first GIFT cycle.
Design	Two-arm trial with quasi-random treatment allocation according to the last digit of chart number.

Setting	Infertility clinic, University of Genoa.
Patients	Included were 187 normally menstruating women undergoing their first GIFT cycle between January and November 1987. Mean female ages were 34 and 33 years, in the short and long protocols, respectively. Diagnostic distributions were similar between groups.
Interventions	1. Buserelin 200 µg IN five times daily with FSH/hMG beginning on cycle day 3 (flare-up). 2. Buserelin 200 µg IN five times daily beginning in the preceding luteal phase (suppression) and followed by FSH/hMG.
Main Outcomes Measured	Cycle cancellation; oocytes retrieved; clinical pregnancy.
Main Results	The only significant difference noted between groups was the higher number of oocytes obtained following the flare-up protocol (8.85 versus 6.85, $p < 0.05$). Cancellation and clinical pregnancy rates were similar. Spontaneous abortion rates were not reported.
Conclusions	No clinically significant differences were noted between groups. However, given the increased duration of treatment with the suppression protocol, the flare-up approach "might be the first choice." However, more patients experienced an "excessive ovarian response" in this group (7:1), raising concerns about an increased risk of ovarian hyperstimulation.

Authors and Year: R. Ron-El et al. (1991)

Title	"Gonadotropins and Combined Gonadotropin-Releasing Hormone Agonist-Gonadotropins Protocols in a Randomized Prospective Study."
Objective	To compare ovarian stimulation with hMG alone versus hMG together with Gn-RHa.
Design	This was a two-arm crossover trial. The method of random allocation was not described.
Setting	Ambulatory care, University Hospital, Tel Aviv, Israel.
Patients	Included were 276 patients undergoing IVF-ET, with no apparent exclusions. Approximately 45% had tubal disease, 30% unexplained infertility, and 15% male factor. Twenty-six patients had two cycles of treatment, and 250 a single cycle. Data from repeat cycles cannot be separated from first cycles.
Interventions	1. Decapeptyl 3.2 mg IM depot + hMG. 2. hMG alone.

Main Outcomes Measured	Cycle cancellation rate; number of hMG ampoules; LH; number of oocytes and embryos; and pregnancy rate. Live birth and ovarian hyperstimulation rates were also reported.
Main Results	Gn-RHa/hMG therapy was associated with lower rates of cycle cancellation (3% versus 27%), greater doses of hMG (43 versus 23 ampoules), higher estradiol and lower LH levels, more oocytes (8.9 versus 7.6), and more embryos (3.9 versus 2.6) than with hMG alone. The pregnancy rate per oocyte was higher (27%) than with hMG alone (13%). Moderate and severe ovarian hyperstimulation were more common with combined therapy (10:1). Multiple pregnancy was also more common with Gn-RHa (7:1).
Conclusions	Pre-treatment with Gn-RHa improves fertility in IVF programs. One of the most significant "costs" was moderate to severe hyperstimulation. More multiple pregnancies and the need for higher doses of hMG are also important findings.

Authors and Year: E.M. Smith et al. (1989)

Title	"Trial of Support Treatment with Human Chorionic Gonadotrophin in the Luteal Phase After Treatment with Buserelin and Human Menopausal Gonadotrophin in Women Taking Part in an In Vitro Fertilisation Programme."
Objective	To compare hCG luteal support following Gn-RHa ovulation induction versus no treatment in IVF patients.
Design	Quasi-randomized two-arm study comparing hCG luteal support with no treatment in IVF patients receiving Gn-RHa ovulation induction. Method of treatment allocation was by day of hCG ovulatory dose administration.
Setting	Department of Human Reproduction and Obstetrics, Princess Anne Hospital, University of Southampton, Southampton, United Kingdom.
Patients	One hundred and fifteen women attending the IVF unit who had at least one embryo transferred were enrolled in this study. It is not clear whether these were consecutive patients. The mean female age in the hCG group was 32.2 years and in the no-treatment group was 31.9 years. Indications for IVF and the number of patients undergoing their first treatment cycle were similar between groups.
Interventions	1. hCG 2 500 IU 3 and 6 d after the ovulatory hCG dose (10 000 IU). 2. No luteal phase support.
Main Outcomes Measured	Luteal phase serum estradiol and progesterone; implantation; clinical pregnancy; spontaneous abortion; multiple pregnancy.

Main Results	In non-pregnant patients, the mean serum progesterone level on day 12 and the luteal phase length were greater following hCG administration. A mean of 3.16 and 2.91 embryos were transferred per cycle in these treatment groups. The implantation rate following hCG was 18.7% and with no luteal support was 6.9%. Clinical pregnancy occurred in 25/61 cycles with hCG (41%) versus 8/54 cycles with no treatment (15%) ($p < 0.01$). There were three spontaneous abortions and one ectopic pregnancy in each group. With hCG support, 24 babies were born including five sets of twins and one set of triplets. With no luteal support, three babies were delivered, with one set of twins.
Conclusions	hCG luteal support following Gn-RHa ovulation induction significantly enhances implantation and clinical pregnancy ($p < 0.01$).

Authors and Year: A. Trounson et al. (1986)

Title	"The Effect of Progesterone Supplementation Around the Time of Oocyte Recovery in Patients Superovulated for In Vitro Fertilization."
Objective	To determine whether progesterone or hCG administration around the time of oocyte retrieval would improve the chance of pregnancy in IVF patients."
Design	Three-arm randomized trial (method of allocation not described).
Setting	Monash University, Epworth Medical Centre, Melbourne, Australia.
Patients	Forty-two possibly consecutive patients were included during a three-month period.
Interventions	1. 25 mg progesterone in oil 21-24 h post-hCG administration + 50 mg progesterone 35 h post-hCG (n = 14). 2. Supplementary hCG 5 000 IU 24 h after their initial dose (n = 14). 3. No additional treatment (n = 14).
Main Outcomes Measured	Endocrine response; clinical pregnancy.
Main Results	Circulating progesterone was increased in the progesterone group compared with hCG and no treatment. Pregnancy occurred in 4/14 patients in each treatment group, with one miscarriage also in each group.
Conclusions	Supplementation with progesterone or hCG around the time of oocyte retrieval has no apparent effect on IVF outcome.

However, this study had insufficient power to adequately address this question.

Authors and Year: A.B van de-Helder et al. (1990)

Title	"Comparison of Ovarian Stimulation Regimens for In Vitro Fertilization (IVF) With and Without a Gonadotropin-Releasing Hormone (GnRH) Agonist: Results of a Randomized Study."
Objective	To determine which protocol for ovarian stimulation in IVF patients is associated with optimal patient outcomes.
Design	Three-arm clinical trial, method of randomization not described.
Setting	Department of Obstetrics and Gynaecology, University Hospital, Leiclen, Netherlands.
Patients	One hundred and fifty-three women under 41 years of age with infertility due to bilateral tubal disease were studied during their first IVF cycle; all male partners had normal semen analyses. The women were randomized to one of three groups for therapy.
Interventions	1. hMG/hCG alone. 2. Gn-RHa/hMG/hCG, commencing Gn-RHa, day 1 — flare-up. 3. Gn-RHa/hMG/hCG, commencing Gn-RHa mid-luteal phase of previous cycle — suppression. The Gn-RHa used was nasal buserelin 200 μg IN TID.
Main Outcomes Measured	Clinical pregnancy; multiple pregnancy; spontaneous abortion; OHSS.
Main Results	The pregnancy rate was higher in the short flare-up protocol group than in the hMG-only group. A reduction in poor response to stimulation was also observed in the short-protocol group. Numbers of oocytes obtained and fertilization rates were not different among the treatments. The long protocol required significantly more hMG per cycle and a significantly longer treatment period.
Conclusions	The short flare-up protocol for induction of ovulation for IVF appears to be associated with improved outcomes, in terms of increased pregnancy rates and decreased numbers of poor responders, when compared with hMG/hCG alone.

Authors and Year: J.L. Yovich et al. (1985)

Title	"Early Luteal Serum Progesterone Concentrations Are Higher in Pregnancy Cycles."

Objective	To assess the effect of IM progesterone given following oocyte retrieval for IVF, or serum progesterone levels and clinical pregnancy rate.
Design	Two-arm quasi-randomized study using sequential patient allocation.
Setting	University of Western Australia, Perth, Australia and Perth IVF-ET Centre, Perth, Australia.
Patients	One hundred and thirty-seven consecutive patients having their first or second IVF attempt were included.
Interventions	1. Progesterone 50 mg in oil (Proluton®) IM for 5 d (0-4) post-oocyte retrieval. CC-hMG was used routinely for ovulation induction. 2. No luteal support.
Main Outcomes Measured	Serum progesterone; clinical pregnancy.
Main Results	Pregnant patients had higher progesterone levels than non-pregnant patients on days 1, 2, and 3 post-retrieval. Non-pregnant patients receiving IM progesterone had significantly higher circulating levels of progesterone during the first 5 d of the luteal phase. Pregnancy occurred in 5/60 untreated and 11/66 treated cycles (non-significant).
Conclusions	Progesterone administration increases its circulating levels. Clinical pregnancy rates were similar between groups (note small sample size). Relatively higher circulating progesterone levels are required for pregnancy. This last conclusion may be incorrect because pregnancy itself results in higher progesterone levels.

Authors and Year: J.L. Yovich, W.R. Edirisinghe, and J.M. Cummins (1991)

Title	"Evaluation of Luteal Support Therapy in a Randomized Controlled Study Within a Gamete Intrafallopian Transfer Program."
Objective	To determine the efficacy of IM progesterone, hCG, or a combination of the two versus no treatment during the luteal phase of women undergoing GIFT.
Design	Sequential allocation to four treatment arms. The sample size was not reported. The goal of 50 cycles in each arm or evidence of treatment benefit were the limits set for completion.
Setting	Perth IVF-ET Centre, Perth, Australia.

Patients	Between August 1986 and July 1987, 280 consecutive couples were recruited with unexplained infertility and mild endometriosis prior to GIFT.
Interventions	1. No treatment. 2. hCG 1 000 IU IM 4, 7, 10, and 14 d post-retrieval. 3. Proluton® 50 mg IM days 0, 1, 2, 3, and 4 post-retrieval. 4. A combination of hCG and Proluton® in the above doses.
Main Outcomes Measured	Implantation; clinical pregnancy; ongoing pregnancy.
Main Results	Clinical pregnancy rates were not significantly different among groups, though the ongoing pregnancy rate was higher with combined luteal support (progesterone + hCG), 15/51 versus 6/51 (p value not given).
Conclusions	These data support combined progesterone/hCG luteal phase support, but larger trials are required to substantiate this.

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Treatment of Male Infertility: Is It Effective? A Review and Meta-Analyses of Published Randomized Controlled Trials

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Executive Summary

For many couples who have difficulty in reproducing, infertility treatment may be administered to the male or female partner (or to both). The diagnosis may be explicit, pertaining to one given explanation or specific to one partner, or it may be unexplained male (or female) infertility. Motivation to bear children may be deep, and the desire to medically assist is strong; however, an objective assessment of treatments and effects must be carried out.

Random assignment to treatment or no treatment is required to assess the many treatments that could be tried, because some couples might conceive in time if no treatment were given, and experimental bias (in several forms) is difficult to avoid. To identify randomized controlled trials from the literature, a computerized MEDLINE search was done. This was backed up by a manual search of 41 journals over the same time period (1966- December 1990). Detailed data were entered into an ongoing, extensive data base that contains information about the location and source of each study, experimental parameters, outcome measures, outcome, and treatment facts. Data obtained in the literature

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review are reported separately for men and women in *Infertility Treatment: From Cookery to Science. The Epidemiology of Randomized Controlled Trials*, also published by this Commission. Results of meta-analyses concerning male infertility are discussed in this paper.

Quantitative meta-analysis improves precision when individually conducted studies are not in themselves adequate to reveal moderate treatment effects. The results were, nevertheless, disappointing (because of the poor quality of a number of trials). Some differentiation concerning promising/less promising treatment parameters was feasible. Truly randomized controlled studies of treatments in this field of endeavour are in order.

Introduction

Approximately 10% of couples experience infertility (defined as failure to conceive after 12 months) (Vessey et al. 1976), and male factors are responsible for some 30% of cases (Hull et al. 1985).

The majority of men who present with infertility have oligo-asthenoteratozoospermia of unknown cause and treatments for this condition are correspondingly varied and empirical. Moreover, improvements in semen variables (concentration, motility, and morphology) do not necessarily correlate with an increased conception rate. Although the figure of 20 million sperm per millimetre is regarded as the dividing line between oligo- and normospermia (World Health Organization 1980), many men with lower counts are fertile (MacLeod and Gold 1951). Motility is the most important quality of spermatozoa, but often varies considerably in the same individual from sample to sample. Sperm morphology is a very subjective measurement (Freund 1966).

Only about 6% of infertile men have conditions for which specific therapy of confirmed benefit is available (Baker and Burger 1986); for example, the treatment of hypogonadotrophic hypogonadism (Hargreave 1983). However, careful randomized studies are needed for the evaluation of infertility treatment for the bulk of subfertile men whose fertility is reduced but does not completely prevent conception. In this group, pregnancy rates are less than 5% per month (Baker 1986) compared with general community pregnancy rates of 20% (Cramer et al. 1979). The only way of establishing a cause-and-effect relationship with respect to a particular therapy is the randomized controlled trial, whose basic principles are the presence of a control group, randomization to overcome selection bias, and a valid statistical test.

The aim of this study was to analyze existing practice in the study of male infertility therapy and to combine the results of existing studies by the technique of meta-analysis with particular emphasis on the pooled results of the better quality studies. Light and Smith (1971) were among the first to propose pooling original data from various research studies, and Glass

(1976) coined the term "meta-analysis." Because pregnancy rates are low in subfertile patients and because moderate treatment effects may be worthwhile, study population numbers in these trials need to be large. Individual trials often fail to provide unequivocal answers to clinical questions, even when designed and executed appropriately, because of limited sample size and power. The science of meta-analysis has emerged as a useful tool in addressing this problem. This quantitative approach to summarizing evidence has generated significant interest in the medical literature. Although applicable to results from all disciplines, the use of meta-analysis has been widely applied in medicine over the past five years in clinical disciplines (e.g., perinatal care).

We have established, between Leeds and Hamilton, Ontario, a data base of randomized and quasi-randomized trials on the subject of infertility. An epidemiological overview of these data, in particular with reference to the quality of randomized trials in this area, is Vandekerckhove et al. (1993). In this paper, we focus in more detail on the treatment of male infertility.

Materials and Methods

The search strategy used to identify randomized trials is explained in detail in Vandekerckhove et al. (1993). In summary, a computerized MEDLINE search was conducted to identify all registered articles (in all languages) published before 1991 concerned with human infertility. To reduce the risk of missing a significant number of studies via the MEDLINE search, the authors also reviewed manually all articles in 41 journals thought to yield the highest number of studies. The hand search included journals from 1966 onward, so that the whole period covered by MEDLINE (from 1966 to December 1990) would be included. Randomized trials dealing with male infertility were extracted from this literature review. A trial was eligible for inclusion in the data base if it dealt with any aspect of treating male infertility and contained a control group that the authors claimed was generated by a randomization procedure. Trials were classified according to a pre-specified list of "quality" criteria as follows:

1. method of randomization — truly randomized, pseudo-randomized, or not specified;
2. sample size and the presence or absence of a power calculation;
3. study design — single stage or crossover; and
4. outcome: Was pregnancy a measured outcome and, if so, how was pregnancy ascertained (i.e., biochemical, gestational sac or fetal heart on ultrasound scan, or delivery of a baby surviving to discharge)? If pregnancy was an outcome, trials were sub-classified according to whether pregnancy rates were measured

on a per cycle or per patient basis; if determined on a per patient basis, the duration and completeness of follow-up in all groups were recorded.

In this paper, we have concentrated on studies in which pregnancy is an outcome. We have presented pregnancy rates as odds ratios with 95% confidence limits. Where meta-analysis was possible, truly randomized studies were listed first on the quantitative meta-analysis diagrams. More weight should be given to truly randomized studies. Pseudo-randomized trials use a randomization method that could have led to prior knowledge of group allocation by the investigator (e.g., date of birth, case record number, date of presentation, alternate assignment). Among truly randomized non-crossover studies, multicentre studies have been presented first for two reasons. First, multicentre studies are (almost) always larger; therefore, they give more precise results. Second, the authors suspect that these studies are, as a general rule, methodologically superior, as they are less likely to have suffered from interference with the randomization schedule (cheating). Meta-analysis was confined, in the first instance, to the non-crossover studies or data from the first phase of a crossover study if given by the author (e.g., Ronnberg 1980; Bedford and Elstein 1981; AinMelk et al. 1982). M1 relates to the non-crossover data from truly randomized studies only, and M2 to all non-crossover data. A third meta-analysis, called M3, includes crossover studies and relates to a larger number of patients, but as these studies may exaggerate any beneficial effects, M3 must be interpreted with caution. If the odds ratio on the meta-analysis diagram is >1, the first treatment listed performed better; if the odds ratio is <1, the second treatment listed performed better. Where the confidence interval is entirely >1, the first treatment listed performed significantly better (at the 5% level). If the confidence interval is entirely <1, the second treatment listed performed significantly better (at the 5% level).

Meta-analyses were carried out using the Mantel-Haenszel equation (Mantel and Haenszel 1959). Odds ratios were calculated using computer software from the Department of Epidemiology, McMaster University, Hamilton, Ontario. To test for homogeneity of the odds ratios across trials, the Breslow-Day test was used (Breslow and Day 1980). Treatment effects of trials included in a meta-analysis that are not consistent with each other can be the result of differences in patient characteristics, treatment modalities, outcome assessment methods, or chance. However, statistically significant heterogeneity can also be caused by variations in the methodological quality of the trials; the method of randomization, for example, can be an important source of selection bias (Olive 1986). Calculating the homogeneity of the results of different trials is useful for interpreting the size (and even direction) of the final odds ratio after meta-analysis. Trials presented at the top of the figures are less likely to be biased than those listed below.

The authors acknowledge that the data base as presented is incomplete in that it is likely to be biased toward English-speaking countries. Results of unpublished trials will be appended as they become available. Readers are asked to draw to our attention other trials that have been missed. The exercise of writing to authors for more details (e.g., method of randomization when this has been omitted, or the results of the first phase of crossover studies if not started) has already started.

Results

One hundred and seventy-two randomized studies concerning the treatment of male infertility were identified. In 72 of these, pregnancy was a measured outcome. Appendix 1 shows randomized trials of male infertility in which pregnancy was recorded on a per patient basis. Trials are listed by year of publication and alphabetically by the first author's name. The number of patients in each trial, the odds ratios, and the 95% confidence intervals are given along with the method of randomization for each trial. The number of patients pregnant and not pregnant in each treatment group is also presented, as is the duration of follow-up and the method of diagnosing pregnancy (where this has been stated by the author). Appendix 2 presents the results of randomized trials where pregnancy was reported on a per cycle basis. The number of cycles over which the treatment was given is presented instead of the duration of follow-up. All remaining trials in which pregnancy was an outcome are listed in Appendix 3, where studies with insufficient data to calculate an odds ratio, trials with crossover design and no separate information on the first phase of the trial, and trials with multiple comparison groups have been compiled. The number of patients in each trial and method of randomization are presented. Information on trials concerning the treatment of male infertility in which pregnancy was not included among the outcome measures and on trials in which sperm samples (rather than patients) were randomized to receive different *in vitro* preparation procedures and in which the outcome was usually sperm function and "quality" is available from the authors on request.

Of the trials expressing pregnancy as an outcome (Appendices 1, 2, and 3), six (8.3%) were multicentre studies, four were conducted on a national basis, and two were conducted on an international basis. The average number of centres participating was six (range two to eight).

The average sample size of the trials was 72 patients (range 7-381), but multicentre trials averaged a significantly higher number of patients (159 [range 33-368]) than single-centre trials (66 [range 7-381]). Twenty-five of the trials (35%) were truly randomized, 11 trials (15%) were pseudo-randomized, and in 36 trials (50%) the method of randomization was not specified. The control group received no treatment in 13 trials (18%),

placebo in 25 (35%), some other form of treatment in 28 (39%), and a combination of the above in 6 (8%). Nearly half of the trials (47%) used a crossover trial design, and almost a third (31%) used double-blind methodology. A power calculation was made in only three (4%) trials. The duration of follow-up of the trials listed in Appendix 1 varied from 2 to 53 months (average 8). Pregnancy rates were expressed as cumulative conception curves in 14 (20%) of the pregnancy trials. The method by which pregnancy was diagnosed was stated in only 8 of 72 (11%) trials — one by gestation sac and one by fetal heart on ultrasound scan, four by ultrasound scan but not further specified, and two by biochemical testing. Twenty-six (60%) of the trials with calculated odds ratios (Appendices 1 and 2) showed a beneficial effect of the given treatment, but in only four of these (Casper et al. 1983; Wikland et al. 1987; Check et al. 1989; Painvain et al. 1989) did both limits of the 95% confidence intervals exceed one.

A source of funding was stated in 66 trials. Thirty-six were funded by national research bodies, 17 by a drug company, 7 by international research organizations (e.g., World Health Organization), and 6 by local university or hospital grants.

Topics in the treatment of male infertility, where meta-analysis was possible because the same or similar treatments had been used, consisted of the following:

1. clomiphene citrate or tamoxifen versus placebo or vitamin C for oligospermia;
2. oral kallikrein versus placebo for oligospermia;
3. bromocriptine versus placebo for oligospermia;
4. mesterolone or testosterone versus placebo or vitamin C for oligospermia;
5. timing of artificial insemination with donor sperm (AID) using urinary luteinizing hormone (LH) versus basal body temperature (BBT);
6. fresh versus frozen donor semen for AID; and
7. intrauterine insemination (IUI) versus normal coitus or intracervical insemination (ICI) for oligospermia.

The results of the meta-analyses are described below.

Anti-Estrogens in Male Infertility

We have identified ten randomized controlled trials on the use of anti-estrogens in subfertile men. Two of these are not included in the meta-analysis: Paulson's (1979) trial used cortisone acetate for the control group, and the trial of Semczuk et al. (1985) compared two different dosages of clomiphene. Tamoxifen was used by Torok (1985), whereas clomiphene citrate was used in the remaining trials. Placebo was the

control treatment in the trials by Ronnberg (1980), Wang et al. (1983), Torok (1985), AinMelk et al. (1987), and Sokol et al. (1988). Abel et al. (1982) and Check et al. (1989) gave vitamin C to controls, whereas the control patients in the trial by Micic and Dotlic (1985) received no treatment. The dose of clomiphene citrate was either 25 mg or 50 mg, administered orally. The number of patients in the trials ranged from 16 in the trial by AinMelk et al. (1987) to 196 in the multicentre trial of Abel et al. (1982). Four trials were truly randomized (Ronnberg 1980; Abel et al. 1982; Torok 1985; Sokol et al. 1988). A meta-analysis (M3) (Figure 1) that includes the crossover study of Wang et al. (1983) and AinMelk et al. (1987) suggests that this treatment works, with an odds ratio and 95% confidence interval of 2.47 (1.53-3.97). The Breslow-Day test for homogeneity equals 16.4 ($p < 0.02$); therefore, the data are not homogeneous. If we eliminate the crossover trials along with those of Micic and Dotlic (1985) and Check et al. (1989) on the grounds that Micic and Dotlic did not specify the method of randomization and that the trial by Check et al. was not truly randomized, the odds ratio and 95% confidence interval (M1) become 1.27 (0.67-2.40) and the Breslow-Day test now shows homogeneity ($p = 0.16$).

Oral Kallikrein in the Treatment of Oligospermia

Five randomized trials have investigated the effectiveness of oral kallikrein in treating oligozoospermic men (Schill 1979; Bedford and Elstein 1981; Izzo et al. 1984; Micic et al. 1985, 1990). Control patients in the trials by Micic et al. (1985, 1990) received no treatment, whereas placebo was given to the controls in the trials by Schill, Bedford and Elstein, and Izzo et al. Kallikrein 600 units were given orally for periods of seven weeks to six months. The trials by Izzo et al. and Schill were truly randomized. The trial by Bedford and Elstein was a double-blind crossover trial, but only data from the first phase were used for meta-analysis. All but the smallest study showed that oral kallikrein was better than placebo in improving pregnancy rates, but this effect was not significant for any of the studies individually. The confidence intervals of the pooled results (M1) suggest a significant beneficial effect, although not as strong as M3, which includes the trials for which the method of randomization was not stated (Figure 2). The Breslow-Day test shows homogeneity for both meta-analyses ($p = 0.92$ and $p = 0.73$).

Bromocriptine in the Treatment of Oligospermia

Bromocriptine has been tested against placebo for the treatment of oligozoospermic subfertility in three trials, all truly randomized. The trials by Hovatta et al. (1979) and Lunglmayr et al. (1983) were non-crossover studies, whereas that by AinMelk et al. (1982) used a crossover design but separate results of the first phase are given and used for meta-analysis. The combined results of the studies showed no hint of a difference between

bromocriptine and placebo (Figure 3). The Breslow-Day test shows homogeneity ($p = 0.99$).

Androgens (Mesterolone or Testosterone) in the Treatment of Male Subfertility

Hargreave et al. (1984). the World Health Organization Task Force (1989), and Pusch (1989) carried out truly non-crossover, randomized trials. Pusch treated patients with oral testosterone undecanoate. The other trials treated patients with mesterolone. Placebo was used as control in all trials except the Hargreave et al. trial, which used vitamin C. Meta-analysis, whether including M3 or just M1 studies, shows no difference between the two groups (Figure 4). The Breslow-Day test showed homogeneity on both occasions ($p = 0.94$ and $p = 0.90$).

Urinary Luteinizing Hormone Testing Versus Basal Body Temperature in Timing Artificial Insemination with Donor Sperm

Two trials compared urinary LH and BBT methods in timing donor insemination (Barratt et al. 1989; Federman et al. 1990). Both trials show a similar trend toward LH testing, but the combined result (M3) does not approach significance, and confidence intervals are still very wide (Figure 5).

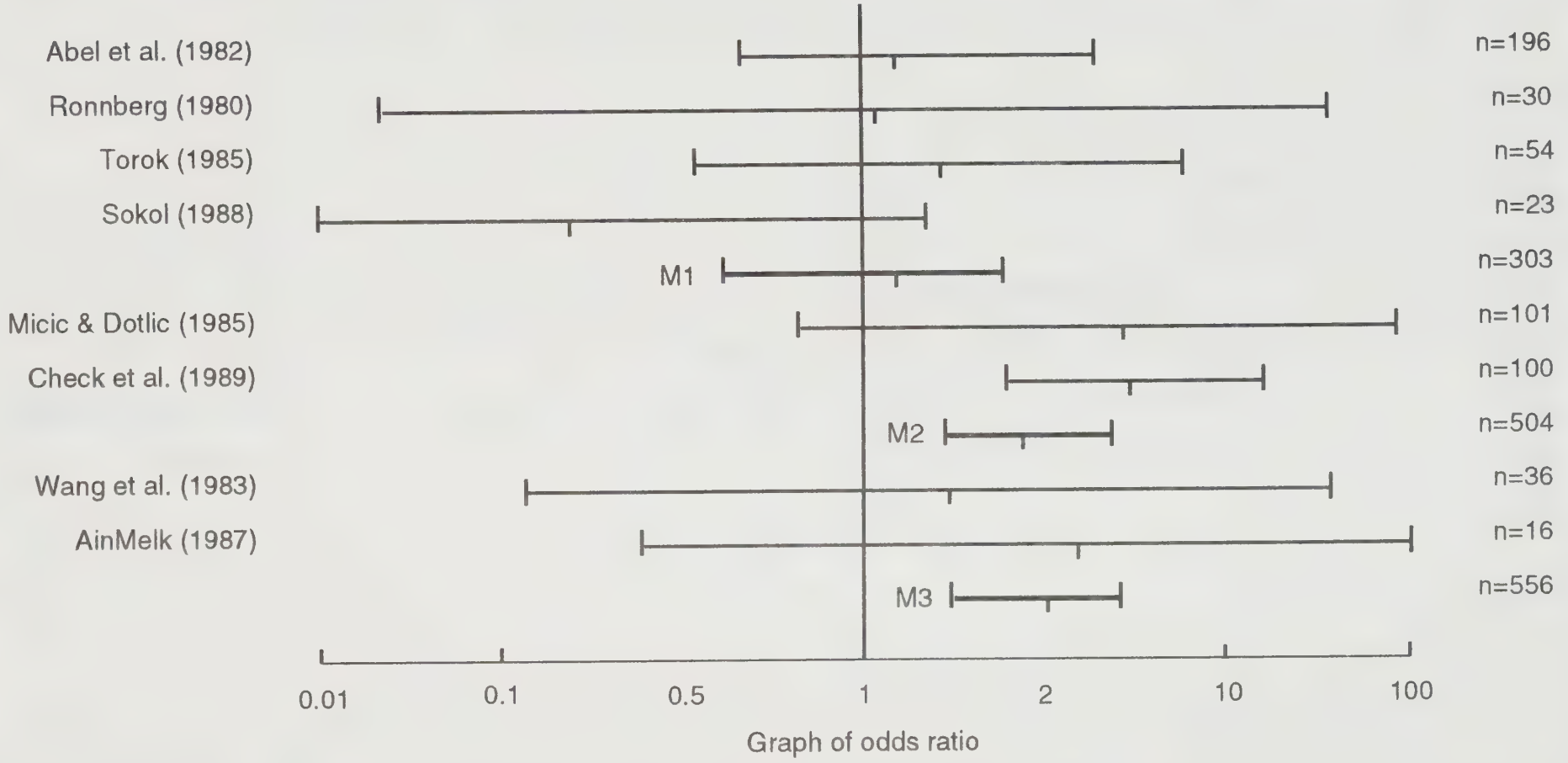
Fresh Versus Frozen Donor Semen for Insemination

The study by Iddenden et al. (1985) is the only one not showing a benefit of fresh semen. In this study, the authors used multiple inseminations of frozen semen in many instances, which may have loaded their results against the benefits of fresh semen. The studies by Richter et al. (1984) and Brown et al. (1988) were crossover studies, and this might have exaggerated the beneficial effects of fresh semen (Figure 6). The Breslow-Day test shows homogeneity ($p = 0.003$).

Intrauterine Insemination with Husband's Sperm Versus Normal Coitus or Intracervical Insemination in the Treatment of Oligospermia

The results of Kerin et al. (1984) are very different from those of other trials in that the subjects were restricted (as far as possible) to one act of intercourse (timed to coincide with ovulation) per cycle, which may have favoured IUI (Figure 7). Although none of the other individual studies reaches significance, the common odds ratio just does. All but one of the eight studies used a crossover design, and only that one study is truly randomized. The Breslow-Day test shows heterogeneity ($p = 0.04$).

Figure 1. Anti-Estrogens vs Placebo/Vitamin C for Oligospermia



Note: M_1 refers to truly randomized, one-phase trials only (in crossover trials, only data from the first phase are used). M_2 includes quasi-randomized trials and trials for which the method of randomization was not specified. M_3 includes all of the above trials and crossover studies (where no separate data from the first phase are available).

Figure 2. Oral Kallikrein vs Placebo for Oligospermia

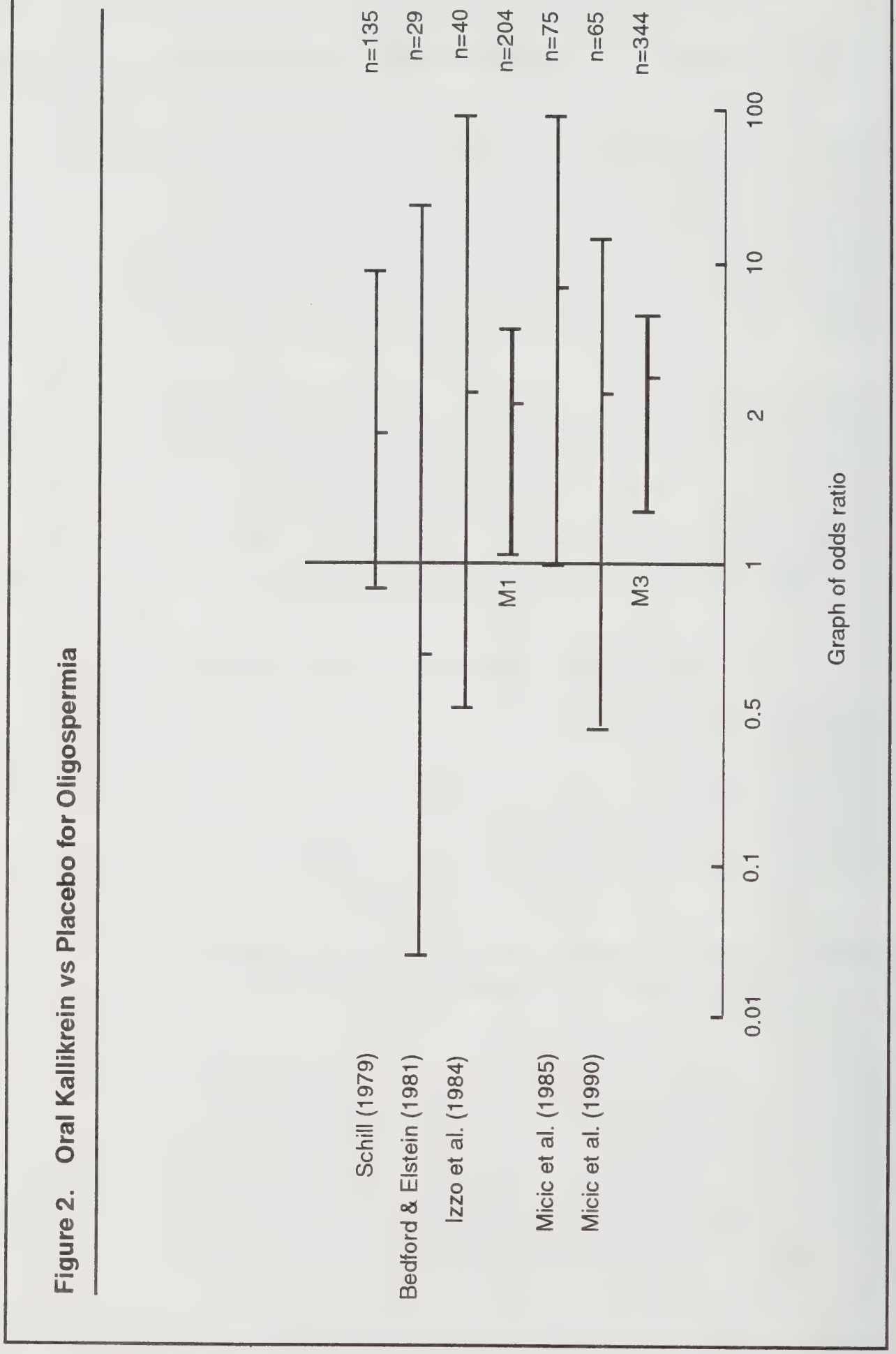


Figure 3. Bromocriptine vs Placebo for Oligospermia

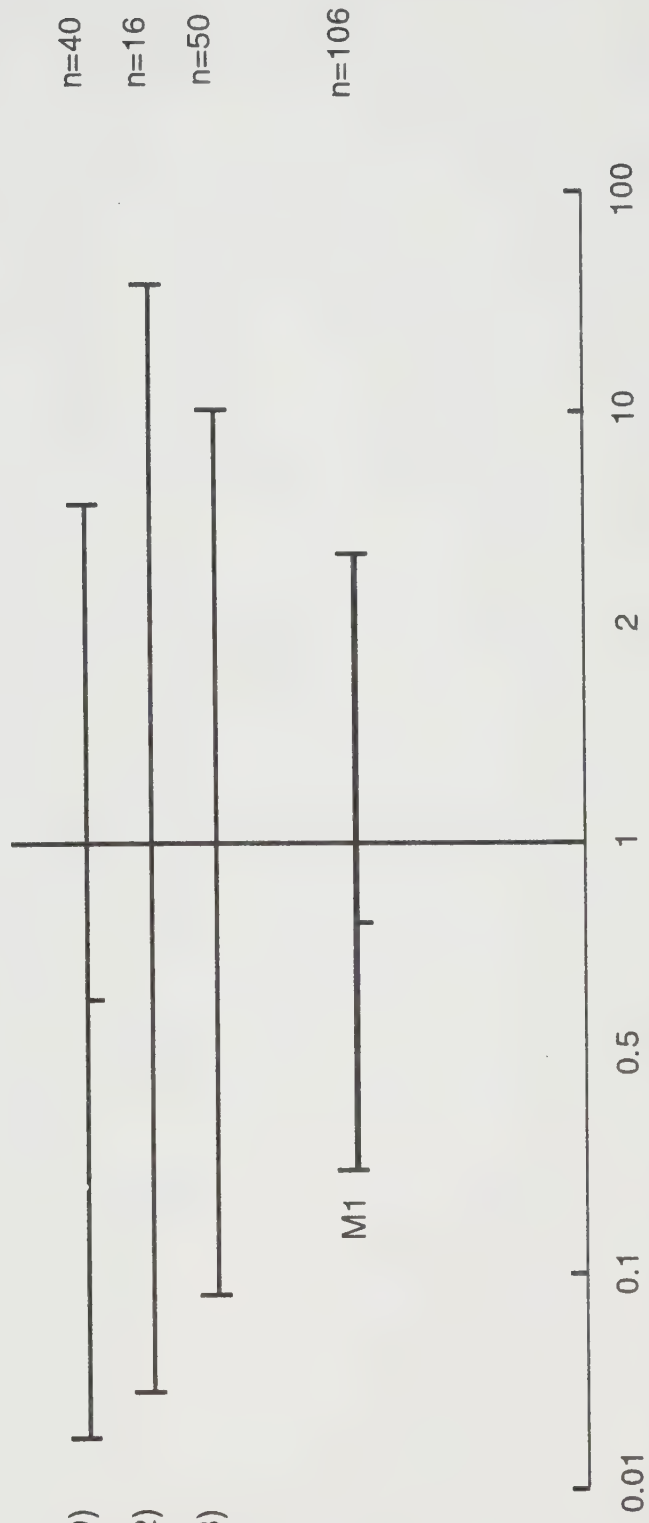


Figure 4. Androgens vs Placebo/Vitamin C for Oligospermia

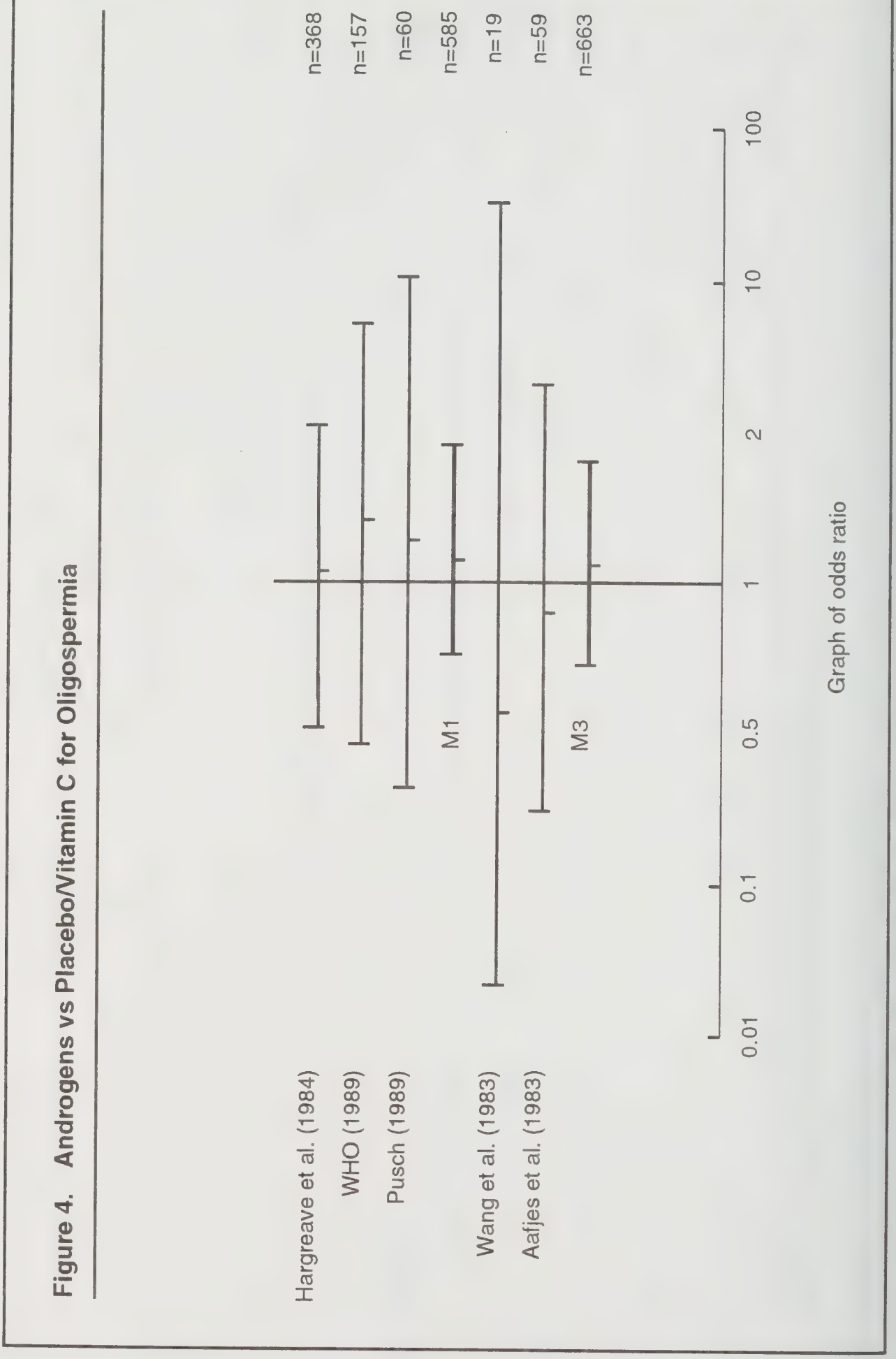


Figure 5. Urinary LH vs BBT for the Timing of AID

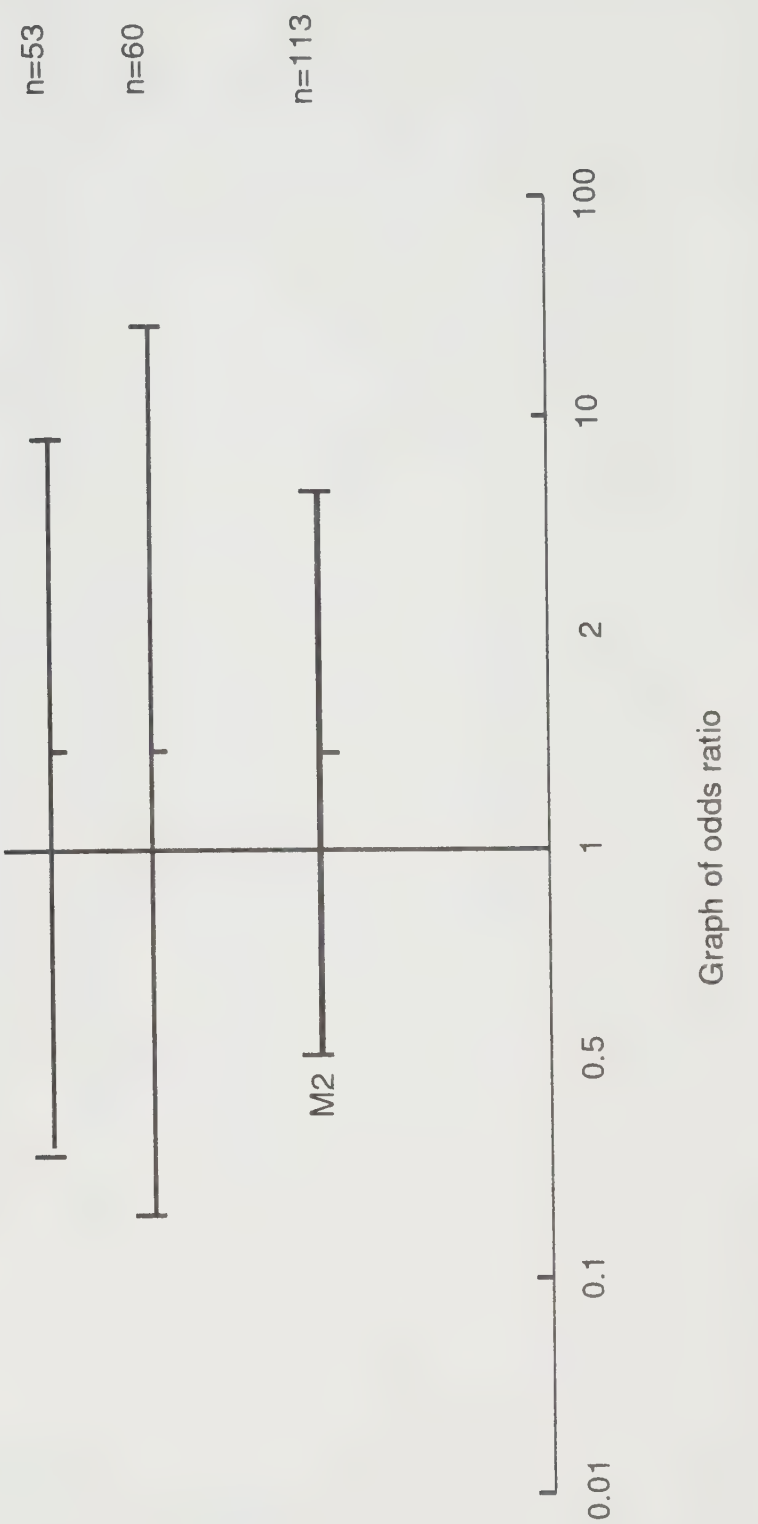


Figure 6. Fresh vs Frozen Donor Semen for Insemination

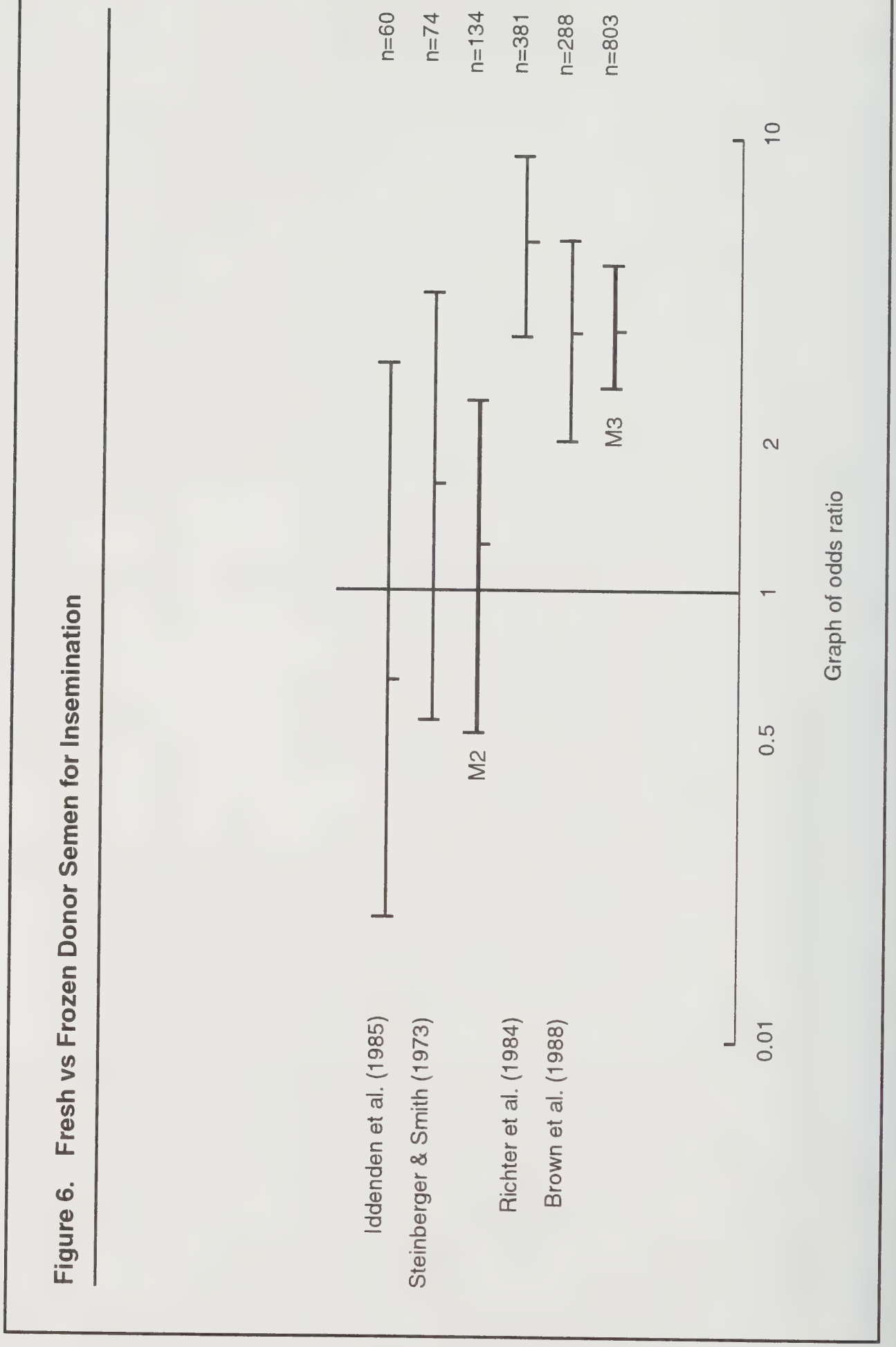
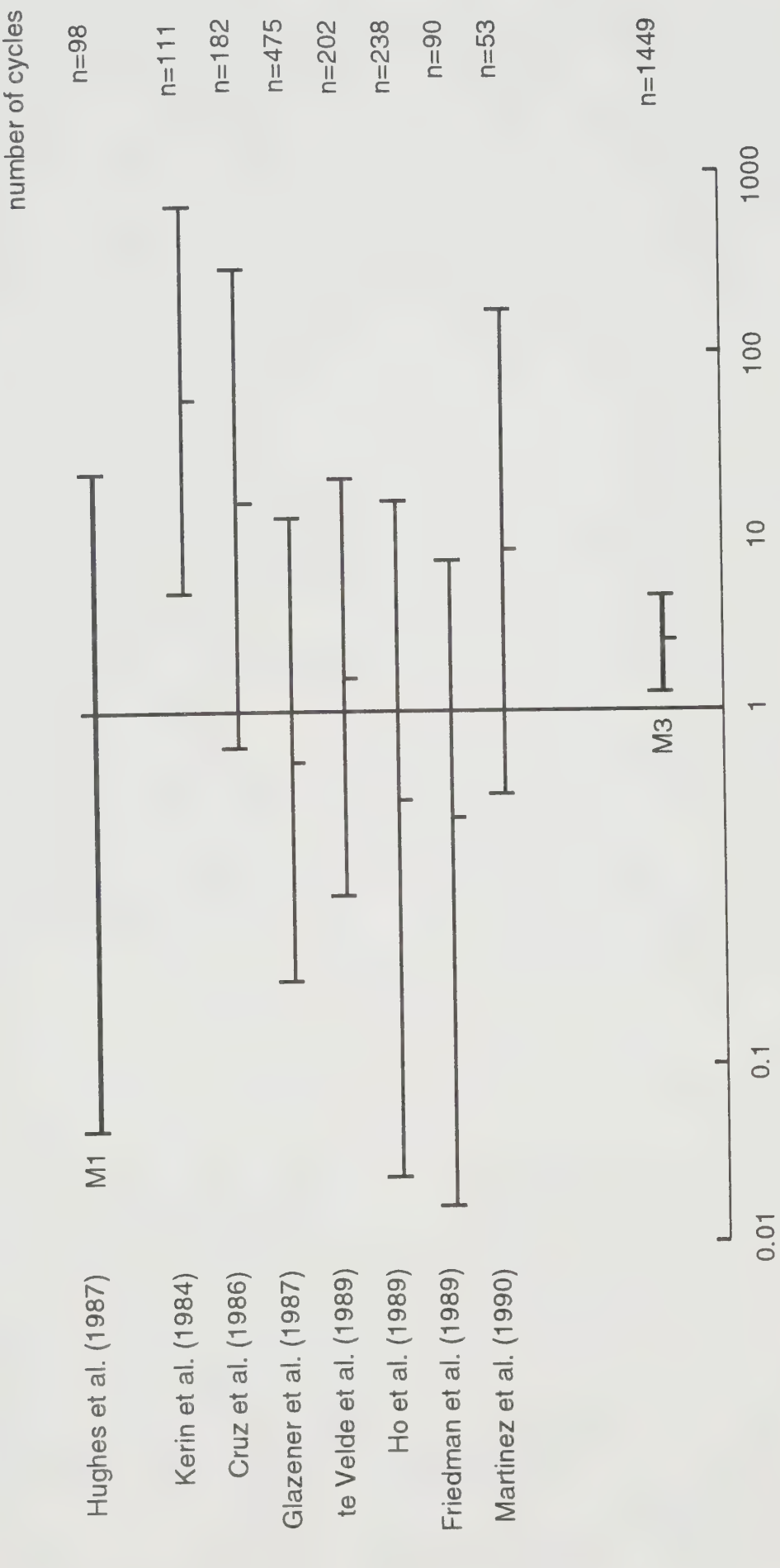


Figure 7. IUI vs Coitus/ICI for Oligospermia



Other Treatments for Male Infertility

Many important questions cannot yet be examined by meta-analysis. Thus, it remains uncertain whether testicular vein ligation for oligozoospermia associated with varicocele is of benefit. Only one randomized trial (Nilsson et al. 1979) examined this issue (the method of randomization was not specified), and a negative result was obtained at the 5% level. Many non-randomized studies have examined this important issue in male infertility. The Japanese study by Okuyama et al. (1988) may be important, as it was a large study of varicocele ligation with prolonged follow-up and a positive result. The controls were men who refused surgery; those who agreed to surgery were assigned to the "treatment" group.

The problem of male immunological infertility has been investigated by four authors in trials with pregnancy as an outcome, but the studies are so different that they do not lend themselves to meta-analysis. Katz and Newill (1980) compared two steroid regimes and concluded that high-dose short-course methylprednisolone therapy is effective in treating infertility associated with antisperm antibodies. Haas and Manganiello (1987) compared methylprednisolone with placebo, whereas Hendry et al. (1990) compared steroids with placebo in a double-blind crossover trial. These two studies found a higher pregnancy rate in patients treated with steroids. Luisi et al. (1982) gave levamisole, a drug with a modulating effect on the immune system, to men with antisperm antibodies and reported pregnancies in the treated group, but the data were insufficient to calculate odds ratios. The only study comparing gamete intrafallopian transfer (GIFT) with *in vitro* fertilization (IVF) for male infertility (Leeton et al. 1987) showed a positive result that was not significant at the 5% level. No study compared GIFT or IVF with no treatment.

Discussion

Infertility treatment is often instituted without proof of its effectiveness, and many treatments with limited scientific credibility have been offered to infertile men. The use of largely unproven treatments for infertility can result in inefficient use of public health funds, may delay effective therapy, and is not free of risks or side-effects in some cases. Unfortunately, this subject has received little scrutiny in unbiased studies, especially those with pregnancy as an outcome. This is in contrast to a vast literature composed of uncontrolled studies (e.g., 325 references to male infertility in MEDLINE alone for 1990). Furthermore, the studies identified suffer from a small sample size, and only a minority uses truly randomized methods.

When pregnancy is an outcome, duration of follow-up should be sufficient to expose any treatment effect. Follow-up of subfertile men has shown that when conception occurs it does so within 6 months in approximately 60% of cases and within 18 months in 80% of cases (Baker and Burger 1986). It is important to allow adequate time not only for pregnancy to occur but also for similar follow-up rates between the compared groups. Analysis of fertility data using cumulative conception curves by life-table analysis is optimal (Peto et al. 1977). The method by which pregnancy is diagnosed, and subsequently counted as a "successful outcome," is also omitted from most studies. Crossover design is often used, but this is inappropriate for studies in which cases may be excluded from the second phase of treatment because they succeeded in the first phase of treatment. This biases the subsequent comparison by exaggerating positive effects; thus, a spurious statistically significant result may be found.

Another problem with infertility trials is that their confidence limits are wide, even after combining them for meta-analysis where possible. In the case of treatments that have minimal side-effects and low cost, moderate or even small beneficial effects would be worthwhile.

The low number of randomized trials concerned with male infertility and the poor quality of those that have been carried out compare unfavourably with studies in other subjects, such as oncological, cardiovascular, and perinatal studies. Cardiovascular studies, and oncological studies in particular, are characterized by a large number of multicentre studies. We prefer these multicentre trials with centralized randomization not only because they are usually more powerful but also because we can be more confident that interference with the randomization schedule (cheating) did not occur. The recent structured overview of clinical trials of homeopathy treatment showed that most single-centre trials produced positive results for the homeopathic treatment of intestinal ileus in contrast with the multicentre trial, which refuted the beneficial effects claimed by the earlier single-centre studies (Kleijnen et al. 1991). Such studies are seldom used to investigate male subfertility, the Hargreave et al. (1984) study being a major exception. Publication bias, interestingly, does not seem to have significantly affected the results presented, as only a small number of individual trials show a positive result.

Few conclusions can be drawn about the treatment of male infertility. Management of patients with oligozoospermia should begin with a search for treatable causes (e.g., hypogonadotropic hypogonadism), or cases with a hopeless prognosis (e.g., Sertoli Cell Only Syndrome). In many cases, no cause can be found and empiric treatment must be considered. In most cases, insufficient trials have been carried out to give a precise answer (e.g., varicocele ligation). Where meta-analysis is possible to high degrees of precision, we tend to find that many poor-quality trials are included, thereby reducing the accuracy of any conclusions. The use of anti-estrogens to stimulate Leydig cells in idiopathic oligozoospermia is a good

example of this problem. Both clomiphene citrate and tamoxifen are well-tolerated, inexpensive treatments. Meta-analysis of the results of all seven relevant studies appears to show a significant beneficial effect. However, the better (truly randomized) studies (Ronnberg 1980; Abel et al. 1982; Torok 1985; Sokol et al. 1988) show much smaller, non-significant beneficial effects, whether assessed singly or in combination (combined odds ratio 1.27 and 95% confidence interval 0.67-2.40). Therefore, we conclude that this is an interesting therapy that deserves wider assessment through randomized controlled trials. It seems likely that even if a benefit is confirmed by a larger number of high-quality studies, the size of this effect will not be as great as the massive effect suggested by the meta-analysis that includes the poorer-quality studies.

We are more sceptical about another form of therapy that appears to be effective upon superficial reading of the meta-analysis: the use of oral pancreatic kallikrein, a kinin-releasing proteinase. The kallikrein-kinin system is thought to play a part in regulating sperm motility, migration, and metabolism (Schill 1979). This therapy can be given orally or parenterally with few side-effects. The combined results appear to support the theory that kallikrein has a place in treating men with oligozoospermia, but we remain uneasy about this conclusion. Only two of the studies were truly randomized, and neither of these was a multicentre study, which we regard as superior. Those who remain open-minded about this therapy should test its effectiveness through better-quality studies.

Meta-analysis of eight studies that have compared IUI with coitus or ICI for oligospermia appears to suggest that IUI is beneficial (Figure 7); however, all but the study by Hughes et al. (1987) used a crossover design, which can skew the results.

Meta-analysis has been more useful in proving treatment ineffectiveness than in confirming effectiveness. Prolactin seems to play a role in spermatogenesis and hormonal secretions (Bartke 1977), and an inverse relationship has been found between serum prolactin level and sperm count in oligozoospermic men (Koskimies et al. 1978); however, the practical significance of this finding is limited because the trials by Hovatta et al. (1979), AinMelk et al. (1982), and Lunglmayr et al. (1983) showed that bromocriptine had no effect over placebo on sperm analysis and pregnancy rates.

The results of trials involving continuous low-dose androgen treatment of male infertility suggest that this therapy is also totally ineffective. Biochemical timing of donor insemination is another treatment with no proven benefit.

Conclusions

Meta-analysis can resolve uncertainty in clinical science, but the number and quality of randomized studies concerning male infertility are insufficient to allow firm conclusions in most cases. Whereas bromocriptine and androgen therapy are confirmed to be ineffective by this technique, other important questions remain unanswered. In the case of kallikrein, IUI and anti-estrogen therapy, sufficient studies have been carried out, but they are of insufficient quality. In the case of varicocele ligation or steroid immunosuppressive therapy, existing studies are both qualitatively and quantitatively inadequate. There is a pressing need for good-quality studies that are truly randomized, are one stage, have had a power calculation, have had follow-up over a sufficient period, and are (preferably) multicentre studies. The data base created by the present investigators is not static, and information will be added as a result of writing to authors for more details and by appending the results of new trials as they become available and those of previous trials that have been missed. The authors are particularly anxious to hear about trials published in non-English language journals and those that have not been published at all.

Appendix 1. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome on a Per Patient Basis

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Pryor et al.	London UK 1978	Arginine vs. placebo for oligospermia	64	0.81 (0.07-8.80)+	TR	2	33	2	27	NS	3
Hovatta et al.	Helsinki Finland 1979	Bromocriptine vs. placebo for oligospermia	40	0.47 (0.01-7.66)	TR	1	19	2	18	NS	3
Nilsson et al.	Goteborg Sweden 1979	Ligation of varicocele or not for oligospermia associated with varicocele	96	0.39 (0.09-1.60)	NS	4	47	8	37	NS	36-74
Paulson	Durham USA 1979	Cortisone acetate vs. clomiphene for oligospermia	40	0.20 (0.02-1.38)	PR	2	18	7	13	NS	9
Schill	Munich Germany 1979	Kallikrein vs. placebo for oligospermia	135	3.05 (0.89-10.95)	TR	14	34	5	37	NS	12

Katz and Newill	London UK 1980	Comparison of two steroid regimes for male immunological infertility	7	20.0 (0.58-3641)#	PR	4	3				
Ronnberg	Oulu Finland 1980	Clomiphene vs. placebo for normo- and oligospermia	30	1.07 (0.03-44.94)+	TR	1	13	1	14	NS	3
Bedford and Elstein	Manchester UK 1981	Kallikrein vs. placebo for oligospermia	29	0.75 (0.02-32.55)+	TR	1	12	1	9	NS	3
Sharlip	San Francisco USA 1981	Comparison of two surgical techniques of vasovasostomy	19	0.66 (0.04-8.34)	PR	6	3	6	2	NS	13
Abel et al.	Multicentre Scotland 1982	Clomiphene vs. vitamin C for male infertility	196	1.46 (0.57-3.76)	TR	15	78	10	76	NS	9
AinMelk et al.	Sherbrooke Canada 1982	Bromocriptine vs. placebo for oligospermia	16	1.00 (0.02-47.27)+	TR	0	6	0	6	NS	4
Aafjes et al.	Rotterdam Netherlands 1983	Mesterolone vs. placebo for oligospermia	59	0.94 (0.18-4.73)+	TR	4	23	5	27	NS	6
Lunglmayr et al.	Vienna Austria 1983	Bromocriptine vs. placebo for oligospermia	50	1.00 (0.09-11.15)	TR	2	23	2	23	NS	3

Appendix 1. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Baker et al.	Melbourne Australia 1984	Erythromycin vs. placebo for asthenospermia	90	3.18 (0.52-24.63)+	TR	6	34	2	36	NS	2
Hargreave et al.	Multicentre Scotland 1984	Mesterolone vs. vitamin C for male infertility	368	1.06 (0.58-1.91)	TR	34	142	28	124	NS	12
Izzo et al.	Pisa Italy 1984	Kallikrein vs. placebo for oligospermia	30	3.21 (0.24-90.80)#	TR	2	13	0	14	NS	3
Iddenden et al.	London UK 1985	Fresh vs. cryopreserved semen for AID	60	0.73 (0.21-2.47)*	NS	10	10	23	17	NS	12
Micic and Dotlic	Belgrade Yugoslavia 1985	Clomiphene vs. no treatment for oligospermia	101	7.36 (0.87-162.9)#	NS	7	49	0	45	NS	9
Micic et al.	Belgrade Yugoslavia 1985	Kallikrein vs. no treatment for oligospermia	75	8.37 (0.99-184.6)#	NS	9	36	0	30	NS	6

Semczuk et al.	Lublin Poland 1985	Comparison of two doses of clomiphene (50 mg vs. 100 mg) for oligospermia	22	4.10 (0.33-110.9)#	NS	4	10	0	8	NS	6
Torok	Kecskemét Hungary 1985	Tamoxifen vs. placebo for oligospermia	54	2.20 (0.53-9.34)	TR	9	18	5	22	NS	12
Comhaire et al.	Multicentre International 1986	Doxycycline vs. placebo for oligospermia with genital tract infection	33	1.33 (0.07-42.00)	TR	2	18	1	12	NS	5
Haas and Manganiello	Oklahoma City USA 1987	Methyl-prednisolone vs. placebo for male immuno-logical infertility	43	2.47 (0.19-69.26)	TR	3	17	1	14	NS	3
Melis et al.	Pisa Italy 1987	AIH + clomiphene vs. AIH only for oligospermia	90	0.86 (0.19-3.78)+	NS	5	43	5	37	NS	6
Hogerzeil et al.	Amsterdam Netherlands 1988	Home vs. clinic inseminations for AID	53	0.96 (0.28-3.27)+	NS	13	16	11	13	NS	6
Micic	Belgrade Yugoslavia 1988	Kallikrein and antibiotics vs. antibiotics only for oligospermia with genital tract infection	120	2.24 (0.88-5.81)	NS	21	43	10	46	NS	3

Appendix 1. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Sokol et al.	Los Angeles USA 1988	Clomiphene vs. placebo for oligospermia	23	0.12 (0.01-1.87)	TR	1	10	4	5	NS	12
Barratt et al.	Sheffield UK 1989	Urinary LH vs. BBT for timing of insemination in AID	53	1.47 (0.34-6.53)	NS	7	20	5	21	NS	6
Check et al.	Philadelphia USA 1989	Clomiphene vs. vitamin C for male partner in unexplained infertility	100	7.25 (2.59-20.90)	PR	29	21	8	42	NS	8
Painvain et al.	Rome Italy 1989	Comparison of two different volumes of frozen sperm for AID	210	2.91 (1.52-5.58)	NS	55	55	23	77	BIOCH	8
Pusch	Graz Austria 1989	Oral testosterone-undecanoate	60	1.62 (0.34-7.98)	TR	6	24	4	26	NS	3

		vs. placebo in oligospermia									
World Health Organization Task Force	Multicentre International 1989	Mesterolone vs. placebo for oligospermia	157	1.61 (0.50-5.45)*	TR	15	89	5	48	NS	8
Hovatta et al.	Helsinki Finland 1990	DIPI vs. IUI combined with ovarian stimulation for male unexplained and endometriosis-associated infertility	124	0.69 (0.29-1.64)	NS	15	48	19	42	NS	4
Micic et al.	Belgrade Yugoslavia 1990	Kallikrein vs. no treatment for oligospermia associated with varicocele	65	2.82 (0.46-21.73)	NS	7	31	2	25	NS	3

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: AID, artificial insemination with donor sperm; AIH, artificial insemination with husband's sperm; BBT, basal body temperature; LH, luteinizing hormone; DIPI, direct intraperitoneal administration; IUI, intrauterine insemination.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes one was added to all the groups);
*, more treatment groups were assigned in the trial but they are combined here to make a 2 × 2 table.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; BIOCH, biochemical.

Appendix 2. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome on a Per Cycle Basis

Author(s)	Origin/year	Evaluation	No. of patients (cycles)	Result	Method of randomization	Treatment group		Control group		Diagnosis of pregnancy	Duration of follow-up (months)
						No. pregnant	No. not pregnant	No. pregnant	No. not pregnant		
Casper et al.	Multicentre Canada 1983	hCG vs. placebo for luteal support in AID	? (74)	4.74 (1.00-23.83)	TR	12	27	3	32	USS-NS	1
Hughes et al.	Ottawa Canada 1987	IUI vs. ICI for oligospermia	20 (63)	0.97 (0.02-37.4)#	TR	0	32	0	31	NS	3
Leeton et al.	Melbourne Australia 1987	GIFT vs. IVF for male infertility	14 (14)	1.00 (0.05-17.24)	PR	2	5	2	5	NS	1
Wikland et al.	Goteborg Sweden 1987	Self-migration method vs. swim-up for sperm preparation in IVF	80 (80)	4.61 (1.07-22.7)	NS	13	31	3	33	NS	1
Baerthlein et al.	Bethesda USA 1988	Simplified vs. complicated method of sperm preparation for AID	42 (201)	1.08 (0.37-3.17)	NS	8	85	10	98	USS-NS	6

Leong et al.	Happy Valley Hong Kong 1988	GIFT + IVF-ET vs. GIFT alone for male infertility	8 (8)	1.50 (0.03-81.25)#	PR	0	3	0	5	USS-FH1	
Tanphaichitr et al.	Ottawa Canada 1988	Comparison of two sperm preparation methods in IVF	40 (40)	1.59 (0.18-15.88)	PR	3	17	2	18	NS	1
Cohen et al.	Atlanta USA 1990	Low-dose immuno-suppression with methyl-prednisolone vs. no treatment in IVF with partial zona dissection for male infertility	37 (44)	8.27 (0.76-208.5)	PR	7	11	1	13	USS-FH	1-2
Federman et al.	Madison USA 1990	Urinary LH vs. BBT for timing of inseminations in AID	60 (264)	1.43 (0.13-15.7)+	NS	2	23	2	33	NS	1

Notes: Calculated odds ratios with 95% confidence intervals.

Evaluation: hCG, human chorionic gonadotropin; AID, artificial insemination with donor sperm; IUI, intrauterine insemination; ICI, intracervical insemination; GIFT, gamete intrafallopian transfer; IVF, *in vitro* fertilization; ET, embryo transfer; LH, luteinizing hormone; BBT, basal body temperature.

Result: +, crossover trial (data analyzed before groups were crossed over if sufficient data);
#, no pregnancy in one of the groups (for statistical purposes one was added to all the groups).

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

Diagnosis of pregnancy: NS, not specified; USS-NS, ultrasound scan — not specified; USS-FH, ultrasound scan — fetal heart on scan.

Appendix 3. Randomized Trials for Male Infertility Treatment: Pregnancy Outcome — Remaining Trials

Author(s)	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Berger and Taymor	Boston USA 1971	hMG vs. placebo for ovarian stimulation and timing of insemination in AID	20	CO	NS
Wieland et al.	Cleveland USA 1972	Cisclomiphene vs. placebo for oligospermia	11	CO ID	NS
Friberg and Gemzell	Uppsala Sweden 1973	Comparison of two methods of sperm cryopreservation for AID	83	CO	NS
Steinberger and Smith	Houston USA 1973	Fresh vs. frozen semen in AID	74	CO	NS
Schill and Littich	Munich Germany 1981	Addition of kallikrein to split ejaculates in AIH for oligospermia	48	CO ID	TR
Luisi et al.	Pisa Italy 1982	Levamisole vs. placebo for male immunological infertility	25	CO ID	TR
Wang et al.	Hong Kong 1983	Comparison of placebo, clomiphene, mesterolone, pentoxifylline, and testosterone for oligospermia	46	CO MCG	NS
Kerin et al.	Woodville Australia 1984	IUI vs. coitus in oligospermia	35	CO	NS

Richter et al.	Madison USA 1984	Fresh vs. frozen semen in AID	381	CO	PR
Francavilla et al.	L'Aquilla Italy 1985	IUI vs. coitus for negative post-coital test	26	CO	NS
Cruz et al.	New Brunswick USA 1986	IUI vs. ICI (combined with ovulation induction) for oligospermia	49	CO	NS
Irvine et al.	Edinburgh UK 1986	IUI vs. ICI in unexplained infertility	21	CO	NS
AinMelk et al.	Sherbrooke Canada 1987	Tamoxifen vs. placebo for oligospermia	16	CO	NS
Glazener et al.	Bristol UK 1987	IUI vs. coitus for negative post-coital test	46	CO	PR
Brown et al.	Madison USA 1988	Fresh vs. frozen (using new cryopreservation method) insemination in AID	288	CO	NS
Micic et al.	Belgrade Yugoslavia 1988	Pentoxifylline vs. observation for oligospermia	90	ID	NS
Blumenfield and Nahhas	Haifa Israel 1989	Follicular fluid vs. placebo-treated sperm in IUI for oligospermia	31	CO	NS

Appendix 3. (*cont'd*)

Author(s)	Origin/year	Evaluation	No. of patients	Trial problem	Method of randomization
Claraz et al.	Lyon France 1989	hCG or not for ovulation and timing of insemination in AID	77	ID	NS
Clark and Sherins	Atlanta USA 1989	Testolactone vs. placebo for oligospermia	33	CO	TR
Friedman et al.	Boston USA 1989	IUI vs. ICI for oligospermia	19	CO	NS
Ho et al.	Hong Kong 1989	IUI vs. coitus for oligospermia	47	CO	PR
Remohi et al.	Orange USA 1989	Percoll gradient vs. swim-up for sperm preparation (in IUI)	186	ID	NS
te Velde et al.	Utrecht Netherlands 1989	IUI vs. coitus for oligospermia	30	CO	NS
Byrd et al.	Dallas USA 1990	IUI vs. ICI of cryopreserved sperm in AID	154	CO	TR
Comhaire	Gent Belgium	Testosterone vs. placebo for oligospermia	25	CO	TR

Gerhard et al.	Heidelberg Germany 1990	Comparison of native, washed, or kallikrein-treated semen for AIH vs. coitus	172	MCG	NS
Hendry et al.	Multicentre UK 1990	Steroids vs. placebo for male immunological infertility	43	CO	NS
Martinez et al.	Amsterdam Netherlands 1990	Clomiphene vs. spontaneous cycles and IUI vs. coitus in 4 combinations	40	CO MCG	NS
Patton et al.	Portland USA 1990	IUI vs. ICI in AID	26	CO	NS

Notes: Incomplete data; crossover trial design with insufficient data.

Evaluation: hMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; AID, artificial insemination with donor sperm; AIH, artificial insemination with husband's sperm; IUI, intrauterine insemination; ICI, intracervical insemination.

Trial problem: MCG, multiple comparison groups (more than two); ID, insufficient data; CO, crossover.

Method of randomization: TR, truly randomized; PR, pseudo-randomized; NS, not specified.

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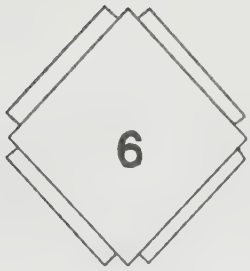
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Adverse Health Effects of Drugs Used for Ovulation Induction

John Jarrell, Judy Seidel, and Philip Bigelow



Executive Summary

A comprehensive literature review and summation of adverse health effects related to the most commonly used methods of ovulation induction were the primary goals of this study. This document is an abridged version of the original manuscript and includes only those references mentioned in the text and the tabular information essential to the discussion. The complete document, which includes other appendices, such as the summary table of adverse health outcomes per reviewed article, and more than 2 500 references, is available from the archives of the Royal Commission on New Reproductive Technologies.

Although many studies report numerous adverse effects, the amalgamation of these data was hampered by the lack of standardized reporting of relevant outcomes and the infrequency of randomized controlled studies with "no-treatment" arms. However, several important conclusions can be derived from the existing literature.

It is clear that many aspects of measurable reproduction can be altered by the administration of clomiphene citrate in animals. Whether these findings can be extrapolated to humans and human health is not known. With respect to human data, reported adverse outcomes range from effects on gastrointestinal and urogenital systems to effects on various aspects of pregnancy.

It appears that the use of human menopausal gonadotropin (hMG) enhances these effects. The most prevalent adverse health effects related to ovulation induction with clomiphene citrate or hMG are summarized in the following table.

This paper was completed for the Royal Commission on New Reproductive Technologies in April 1992.

Adverse Outcomes of Ovulation Induction

Outcome	Clomiphene citrate			hMG*		
	%	No. of studies	No. of patients	%	No. of studies	No. of patients
Combined crude rates						
Hyperstimulation	8.20	1	29/354	7.30	19	1 171/16 103
Abortion	21.60	35	3 550/17 202	25.90	100	8 175/31 618
Ectopic	1.60	4	98/6 225	3.30	37	678/20 624
Stillbirth	1.70	4	55/3 298	6.30	6	64/1 010
Multiple pregnancy	7.90	16	966/12 250	20.75	45	1 783/8 593
Twins	6.50	12	321/4 920	12.70	45	2 318/18 248
Triplets	0.66	4	21/3 158	2.30	29	336/14 710
Quadruplets	0.31	3	14/4 499	0.65	9	76/11 653
Quintuplets	0.11	1	3/2 635	0.51	3	6/1 186
Prematurity	5.10	8	388/7 560	11.80	14	299/2 528
Heterotopic	0.93	1	1/108	2.90	9	38/1 311
Meta-analysis						
Change in sex ratio	94.2 men / 100 women, $p < 0.05$			Not significant		
Congenital malformations	Not significant			Not significant		
Neural tube defects	Odds ratio = 1.86 95% confidence interval (1.2-2.9)**					

* hMG includes all associated treatments except clomiphene citrate.
** Reported rate includes clomiphene, hMG, and other drugs used for ovulation induction.

Introduction

This project focusses on the adverse health effects attributed to some of the most commonly prescribed medication used in the management of infertility. Not only are the drugs used widely, but they are among the most powerful pharmaceutical agents acting on the reproductive system. In undertaking a review of the adverse effects, two major observations can be made: first, that specific interest in adverse effects as a major focus of study has been minimal at best and, second, that perceptual and definitional difficulties persist in what constitutes an acceptable physiologic response rather than a severe adverse outcome.

Interest in the management of infertility has been expanding at a remarkable rate over the past decade. There are many reasons for the expansion, including such arguments as the demographics of the baby boom, the agenda of the provider, and a professional interest in the reproductive process.

Perhaps it is not remarkable that reported interest in the therapeutics of infertility is primarily directed toward the pursuit of successful and effective treatment. What has often been absent from the literature is a concerted effort to capture some of the relevant adverse effects of treatment. Until recently, one of the most significant reasons for this is the lack of standardized reporting of relevant adverse outcomes. For example, there is no way to measure the relative frequency of significant multiple pregnancies due to human menopausal gonadotropin (hMG) because such reporting is not required. Perhaps this is ironic, since there are public hospital requirements for the disclosure of perinatal events. The impact of treatments that lead to severe immaturity would appear to be as significant as those that result in congenital malformation; however, there has been no public policy regarding an organized method for data accrual.

In studying the adverse effects of drugs used for ovulation induction, the perceptual difficulties in defining what constitutes an adverse effect are immediately evident. For the physician treating a young woman with clomiphene citrate, the presence of hot flashes and visual scotomata may be construed more as a physiologic event. For the patient, however, they may be true adverse effects that result in genuine suffering.

This project is a summary of adverse outcomes. As there is no consistent method of reporting such outcomes in a manner that is readily obtainable, no doubt many papers will be missed. Nevertheless, an attempt has been made to capture all relevant reports and, through a process of intense data reduction through meta-analysis, provide a summation of relevant adverse effects.

It is hoped that the information provided by this project will increase interest within the medical profession in the adverse outcomes summarized and enhance the process of obtaining the informed consent of the patients.

Ovulation Induction — Background

Some of the most common causes of infertility are disorders of ovulation. It has been estimated that between 15% and 25% of childlessness in couples is due to anovulation (Hull 1981). Ovulation induction is primarily indicated in the treatment of infertility when anovulation has been established as the cause, or as a preliminary procedure in *in vitro* fertilization (IVF) or artificial insemination (AI). Chemical preparations are administered to stimulate the ovaries and encourage the maturation of multiple follicles. Haighton was the first to observe and describe induction of ovulation in 1797 (Jewelewicz and Gindoff 1988). However, chemical induction of ovulation was not introduced until the 1950s. Numerous chemical agents have been used to induce ovulation both clinically and experimentally, clomiphene citrate and hMG being the two most commonly administered medications.

The actions and administration of clomiphene, hMG, human chorionic gonadotropin (hCG), and follicle-stimulating hormone (FSH) are described below. For further details related to each drug, refer to Appendix 1.

Clomiphene Citrate

Clomiphene citrate is a synthetic, non-steroidal, long-acting estrogen agonist-antagonist that is distantly related to diethylstilbestrol (DES). It was initially developed as an anti-estrogenic, anti-gonadotropic drug and tested for its potential anti-fertility properties. However, Greenblatt et al. (1961) reported that trials in humans resulted in induction of ovulation. Later, clomiphene was introduced for the treatment of anovulation, and it has been administered and studied extensively over the past 30 years.

The exact mechanism of action of clomiphene is currently unknown. It has been suggested that clomiphene stimulates the release of pituitary gonadotropins by inhibiting the negative feedback effect of endogenous estrogens, which in turn mediates ovulation. It is known that clomiphene has a pharmacologic effect on all estrogen-dependent tissue, including tubal transport (Whitelaw et al. 1970).

Clomiphene is usually administered in doses of 50 to 100 mg/day for 5 to 10 days. Lunenfeld et al. (1986) observed that it has a half-life of approximately 5 days, and its activity can be measured in the circulation for up to 30 days after standard treatment. The reported ovulation rates of clomiphene therapy range from 70% to 90%, whereas the reported pregnancy rates range from 30% to 40% (Scialli 1986). It has been argued that the large discrepancy between ovulation and pregnancy rates is attributable to numerous causes ranging from improper patient selection to inadequate implantation support.

Under certain circumstances, clomiphene is used to induce ovulation in combination with various other drugs such as hCG, hMG, estrogens, corticoids, and bromocriptine. Although clomiphene was not properly

evaluated before its introduction into clinical practice, it has generally been classified as a safe drug with few adverse health effects.

Human Menopausal Gonadotropin

Human menopausal gonadotropin is used along with hCG to induce ovulation and pregnancy by stimulating the development and maturation of the ovarian follicle and corpus luteum. Pregnant mare serum gonadotropin (PMSG) was used instead of hMG in the 1930s to study ovulation induction in both laboratory animals and humans. However, it was observed that the administration of PMSG in humans resulted in the formation of antibodies, leading to its discontinued use in clinical settings. Successful induction of ovulation in clinical studies — through the administration of hMG — began in the 1960s.

Because the supply is limited if it is extracted from the human pituitary gland, the purified preparation of hMG is extracted from the urine of post-menopausal women. It contains both FSH and luteinizing hormone (LH), usually at a ratio of 1:1. It is usually administered at the lowest possible dosage for 9 to 12 consecutive days to minimize the risks associated with its use. Once follicular maturation has been achieved, hCG is administered to induce ovulation.

Human Chorionic Gonadotropin

Human chorionic gonadotropin, a hormone consisting of two sub-units, is produced by the placenta and extracted from the urine of pregnant women. It is administered in one large dose to induce ovulation after follicular development occurs through stimulation with hMG, FSH, or clomiphene citrate. The action of hCG is primarily the same as those of LH and FSH. Administration of hCG stimulates the spontaneous mid-cycle LH surge, resulting in ovulation.

Pure Follicle-Stimulating Hormone

Administration of pure FSH for ovulation induction is a relatively recent form of infertility therapy. Extracted from the urine of post-menopausal women, FSH stimulates ovarian follicular growth and maturation. Once the follicles are mature, hCG is administered to stimulate ovulation.

Objectives

This study involved a comprehensive literature review, incorporating the meta-analysis technique where possible, of studies that examine animal and human evidence of potential health effects of the most commonly used drugs in ovulation induction (clomiphene, hMG, hCG, and FSH). The outcomes addressed are the following:

1. For exposed females (animal and human): (a) short-term implications, e.g., hyperstimulation and hot flashes; (b) long-term implications, e.g., cancer, infertility, and cyst formation; and (c) pregnancy complications, e.g., abortion, ectopic, and heterotopic.
2. For offspring (animal and human): (a) congenital malformations, e.g., prevalence and type; (b) multiple births, e.g., prevalence and prematurity; (c) cancer, e.g., prevalence and type; and (d) sex ratio.

Objectives of Meta-Analysis

Meta-analysis has been used in this study to:

1. increase the statistical power for important end points and subgroups;
2. resolve controversy when studies disagree;
3. improve the estimates of effect size; and
4. develop new questions that were not previously posed in the individual studies.

Methods and Materials

The health effects of drugs used in ovulation induction were identified by means of two main processes. The first process involved an extensive literature review and the second a survey of fertility clinics in Canada.

Literature Review

Selection of Drugs

The major drugs used in infertility therapy were identified through consultation with three fertility experts and a brief literature review of the medical factors responsible for infertility and their treatments. Twenty-five drugs were identified. They were divided into four categories: (1) ovulation induction, (2) ovulation suppression, (3) luteal phase, and (4) male factor (see Appendix 1).

Ten of the most commonly used fertility drugs were originally selected. These included clomiphene, hMG, progesterone, Danazol®, bromocriptine, tamoxifen, prednisone, FSH, DES, and hCG. To estimate the number of published articles per drug, a quick computer search was conducted on the MEDLINE and TOXLINE data bases covering the years 1985 to 1991. Given the large volume of articles that resulted from the general search, it was determined that only a subset of three or four drugs could be reviewed

thoroughly. Therefore, the most commonly administered fertility drugs used to induce ovulation — clomiphene, hMG, and FSH, along with hCG, as it occurred with the first three drugs — were selected for review. Additional chemical and trade names of each of these four drugs are listed in Appendix 1.

Design of Search Template

Because many adverse health effects related to the administration of drugs are not specifically indexed in most electronic data bases, a search template was developed so that obscure and improperly indexed adverse outcomes could be retrieved. The search template was constructed so that each drug was thoroughly and consistently searched for each year and in each data base. A drug profile was developed for each drug using the following sources: *The Merck Index*; *Martindale: The Extra Pharmacopoeia*; *Meyler's Side Effects of Drugs: An Encyclopedia of Adverse Reactions and Interactions*; and the *Compendium of Pharmaceuticals and Specialties* (*CPS*). The profile contained information such as synonyms, Chemical Abstracts Service registry numbers, known or suspect adverse effects, patent date, and usage. Development of profiles for both hMG and FSH was hampered by the lack of readily available information from these sources.

To construct and refine the search template, review articles on each of the drugs under investigation were reviewed. A list of adverse health outcomes related to the exposed mothers and offspring for both animals and humans was devised. This list was reduced by grouping outcomes into medical subject heading (MeSH) categories (National Library of Medicine indexing). As well, the physiologic processes involved in infertility and their respective clinical presentations were documented in consultation with three experts and by means of a literature review. These outcomes were included in the MeSH list or were added to the list as specific outcomes. The terms listed in the final search template were selected for inclusion based on the following criteria:

1. adverse outcomes as reported in the literature or through consultation with experts;
2. suspect adverse outcomes as reported in the literature or through consultation with experts;
3. outcomes reported as "side-effects";
4. drug-induced physiologic/hormonal changes; and
5. *in vivo* and *in vitro* toxicologic animal and human studies.

Selection of Data Bases and Information Sources

In an attempt to capture literature from worldwide sources, 15 commercial data bases were selected. (The list of data bases is available from the Commission's archives.) Relevant data bases were identified by consulting the following sources:

- National Library of Medicine (Bethesda, Maryland);
- Reproductive Toxicology Center (Columbia Hospital for Women, Washington);
- Center for Disease Control (Atlanta);
- National Institutes of Health (Washington);
- University of Calgary library;
- University of Calgary toxicologist; and
- Canadian Institute for Scientific and Technical Information (CISTI) (Ottawa).

An attempt to obtain unpublished or non-peer-reviewed literature was made by requesting in-house literature and studies from eight major pharmaceutical companies in Canada and the United States. (The list of information sources is available from the Commission's archives.) In addition, 58 papers presented at the seventh meeting of the European Society of Human Reproduction and Embryology (ESHRE) and the seventh World Congress on *In Vitro* Fertilization and Assisted Procreation, were requested.

Design of Coding Apparatus

Complex coding instruments were designed to incorporate the initial selection criteria and capture relevant adverse health outcomes as reported in the literature. The coding sheet and keys were developed by reviewing a sample of articles on each drug. Once the coding instruments were developed, they were altered only slightly to address novel outcomes and studies as they occurred during the review and coding processes.

Gathering, Coding, and Tabulation

An extensive computer literature search was conducted, using the carefully designed search template and accessing the 15 data bases, covering the period from 1955 to the date of the search. All references were obtained from CD-ROM diskettes or on-line data base services. The references were transferred to a personal computer and into a reference manager software package. A data base on each drug was constructed from the downloaded sources and duplicate references were removed. Each reference was reviewed, and all false-positive hits from the original searches were removed.

A decision to exclude drug-induced physiologic/hormonal changes was made after it was realized that the volume of related material could not be incorporated into this study due to time constraints and the volume of data related to priority adverse outcomes (i.e., known and suspect adverse outcomes). A reference list was made from the new drug data bases, and all obtainable references were acquired from various libraries and agencies in Canada and the United States.

Each article was reviewed, included/excluded, and coded as it was retrieved. Articles were excluded from the study on the basis of the following factors:

- the articles did not discuss adverse outcomes related to the drugs under investigation;
- the articles were unobtainable;
- the articles were unobtainable within the time frame of the study;
- the articles were written in a language that could not be interpreted by the investigators;
- the articles did not report any data or information of importance to the study; or
- the articles dealt purely with hormonal alterations.

Once the articles were coded, they were entered into a statistical software package (SPSS) for analysis. Descriptive statistics and meta-analysis were used to analyze and compile the data. The results are summarized in the following categories:

- all articles identified are listed in a full bibliographic format;
- meta-analysis on specific adverse outcomes was carried out if the selection criteria were met;
- on articles excluded from formal meta-analysis, an opinion is given on what appears to be known and unknown about that outcome from the literature; and
- all "case reports" and "letters" were critically evaluated to identify any early or preliminary evidence with regard to those particular outcomes and their association with ovulation induction drug exposure.

Meta-Analysis

Meta-analysis is a methodology that has been developed to enhance the rigour of assessing the results of investigations that address a single question. The advantage that meta-analysis provides over the conventional narrative review is related to the development of standard techniques for selecting articles, recording results, and combining results across studies. Most narrative reviews are conducted with no systematic approach to obtaining or integrating results, and the conclusions reached may reflect biases introduced through this subjective approach. Meta-analysis, on the other hand, by adhering to previously standardized methods, overcomes the weaknesses of the narrative review.

The methods and materials discussed so far were all developed to enable meta-analysis to be completed on any specific adverse outcome associated with a specific infertility therapy. These methods were developed and tested to ensure their reliability and validity before the results were combined. All of the articles that were coded and entered into the data

base (n = 937) were eligible for the meta-analysis/combined crude rates analysis.

Meta-analysis refers to any standardized methodology in which results from individual studies are aggregated. Such aggregation may take the form of a simple summation of articles that have reported a positive (or negative) effect due to a specific exposure, or may be detailed as computing a combined effect size after controlling for potential confounding factors reported in individual studies. In this study, two major types of meta-analysis were performed: combined crude rates and formal meta-analysis.

Combined Crude Rates

The meta-analyses that allowed for the inclusion of the largest number of articles were those in which an estimation of the crude incidence rate of specific adverse outcomes due to specific exposures was computed. These meta-analyses, termed "combined crude rates," provide an estimate of the incidence rates for specific adverse effects associated with individual infertility therapies on the basis of the total number of patients treated, the total number of treatment cycles, or the total number of pregnancies. Requirements for inclusion in the combined crude rates analyses were mostly established during the development of the coding system. It should be noted that a number of variables were used to code the effect size for each outcome reported in each article. The values coded for these variables were used to determine the combinability of results for each meta-analysis that was completed. Of course, the primary factor determining inclusion was that a crude incidence rate or proportion was recorded. The rule for coding these crude incidence rates was that the crude rate for the specific adverse outcome reported by the authors was clearly stated or could be calculated from the data presented.

Other inclusion and exclusion criteria for the combined crude incidence rates analyses were related to other variables coded for each article. To be included, the variables *ncase* or *ncylase* or both, which refer to the total number of individuals or cycles exposed to the therapy, must have been coded. Numerous variables were used to exclude articles from the analysis. One exclusion criterion was based on the selection of subjects for study; if selection was based on disease status, the article was omitted. Case studies and case series were not acceptable because the selection of subjects for study is made on the basis of the presence of the adverse outcome (making it impossible to determine the incidence rate because the denominator is unknown). Pre-treatment variables that indicated that the outcome may be related to factors not specifically related to the treatment were cause for exclusion. Drug variables that indicated the possibility of complex drug comparisons (within study comparisons of multiple therapies) or interactions (multiple drugs administered to the exposed group) also resulted in exclusion.

Given these criteria, only studies in which the crude rates reported were likely to be attributable to the effect of the therapy under consideration could be combined.

The results from the combined crude incidence rates for each outcome must be interpreted with caution. Even though standardized inclusion and exclusion criteria were applied before the analysis, the potential remains that the overall combined results may have been affected by confounding of extraneous variables and the effect of numerous types of bias. Almost all of the articles that reported crude incidence rates failed to measure or adjust for the effect of other variables that could confound the association under investigation. Even such easily measured factors as age and parity were rarely reported; therefore, in the meta-analysis their effect could not be assessed.

The methodology of the meta-analysis technique, through adherence to explicit protocols at each stage, ensured that internal errors and biases were minimized. The primary limitations of the method pertain to inadequacies associated with the data (studies). One of the most crucial of these limitations may result in what is referred to as selection bias. The aim of the meta-analyses performed was to estimate the magnitude of the effect or association between specific infertility therapies and adverse outcomes. Since articles reporting significant findings (presence of an adverse outcome) would be more likely to be published than those reporting no significant findings, the estimates resulting from the meta-analyses would be biased away from the null. To reduce this potential bias, attempts were made to obtain the results of unpublished literature where possible.

Formal Meta-Analysis

An analysis similar to the combined crude rates, focussing on the incidence rate of neural tube defects (NTDs) and congenital malformations in populations of women exposed to specific infertility therapies, was conducted. For these two adverse outcomes, the expected rates in unexposed populations have been studied. In this analysis these rates were used to calculate the probability of observing the number of malformations reported within each study.

The table in the Executive Summary reports NTDs, congenital malformations, and population rates if reported by the authors. In cases where the unexposed population rates were reported, the probability of observing the reported number of cases, given the sample size (live births and stillbirths), was calculated using the reported rates. In instances in which no unexposed rates were reported by the authors, the probability was computed based on the average of unexposed population rates of all studies in the meta-analysis. The probability values reported (reported as not significant if $p < 0.05$) were based on the assumption that the likelihood of obtaining particular values (observed NTDs and malformations) was binomially distributed.

The data from the individual studies, reporting incidence rates of NTDs and malformations, were aggregated by specific infertility therapy. The total number of births and stillbirths was reported in addition to the total number of NTDs and malformations. Incidence rates for both outcomes and 95% confidence intervals (CIs) were calculated from these aggregate data. The probability of observing this number of cases, given the sample size and using the average unexposed population rates as the probability of an adverse event occurring, was also reported.

A similar procedure was used for the meta-analysis of the outcome of sex ratio. All studies within the data base for which a sex ratio could be calculated and for which the ratio was associated with the infertility therapies under consideration were included. Again, the exact distribution of the number of boys born is binomial, and the probability of observing the birth of a specific number of boys can be determined. The procedure involved first calculating the z-statistic using the formula suggested by Moore and Gledhill (1988). This formula was used with the independent probability of a male child being born of 0.515 based on the theoretical sex ratio of 106:100 (Zarutskie et al. 1989). The aggregate data for sex ratios appear in Table 6. The z-statistics and significance levels are based on the aggregate data compared with the theoretical probability of a male birth.

Few studies reviewed were designed with internal comparison groups that received no treatment. Occasionally, the studies included in the combined incidence rates analyses did report rates of adverse outcomes in unexposed populations. In these studies, however, there was no matching or selection of the control population to enable a true comparison. The few studies investigating the association between NTDs and ovulation induction in which the control group was truly comparable to the exposed or case group were included in a meta-analysis of case-control studies. One prospective study dealing with the association between NTDs and clomiphene exposure, which involved the categorization of women into exposed and unexposed groups before childbirth, was also summarized.

The methodology used for combining odds ratios across studies was the Mantel-Haenszel combined estimate of the common odds ratio. A likelihood-based regression technique was used to determine if a significant interaction of exposure and stratum (study) was present. A significant interaction of exposure would reveal that heterogeneity between the studies was present and that the results from the studies should not be combined. The logistic model was also used to estimate the main effects of exposure to ovulation induction after fitting or controlling for the effect of stratum. The CIs and estimate of the odds ratio are analogous to the Mantel-Haenszel estimate.

The data base of 937 coded studies provided sufficient information to conduct numerous other meta-analyses. However, when data for these analyses were retrieved, few of these studies could have been combined within each group. For example, one type of effect size that was coded pertained to the difference in proportion between two groups. Taking any

one specific outcome, as is required for meta-analysis, there were too few studies in which this difference in proportions was between the same two groups (e.g., difference in the rate of malformations between the clomiphene-exposed group and the group exposed to hMG). Since this information was in the data base but was not suitable for combination within a meta-analysis, the coded information from each study was presented in the form of a table.

Canadian Infertility Clinic Survey: Adverse Outcomes

To obtain information from relevant sources other than those reported in the periodical literature, a questionnaire (Appendix 2) was developed and distributed to fertility clinics in Canada. The major focus of the survey was to obtain information from experts on perceived adverse health effects as they relate to the use of hMG and clomiphene in ovulation induction. Because adverse health outcomes are not often documented by clinics, the perceived occurrence of adverse outcomes was requested. The questionnaire was designed to compile a summary of case reports of infrequent adverse outcomes. The clinics were asked to report on the perceived incidence of the following complications: ovarian pain, ovarian cysts, hyperstimulation syndrome, twins, triplets, spontaneous abortion, congenital malformations, ovarian cancer, and other complications. They were also asked to comment on ovulation induction.

The questionnaires were compiled and analyzed using descriptive statistics and compared with the results obtained from the literature review process.

Results

Literature Search

The computer literature search of the 15 data bases retrieved a total of 4 840 references. Of these, 2 240 were either duplicates or obvious false-positive hits and were removed from the data base. Of the remaining 2 600, 1 651 were obtained; the other 949 were not obtained because they did not fall within the constraints of the study (as mentioned earlier) or they could not be located. In all, over 500 journals were obtained, covering 36 years of publication.

The 1 651 articles obtained (available from the Commission's archives) came from various sources. A total of 937 met the criteria for inclusion in the study and were coded and analyzed. Most of the 714 articles excluded at this stage dealt primarily with hormonal changes. Other articles did not report adverse outcomes or information relevant to the study. Table 1 presents the literature search results from all sources.

Table 1. Literature Search Results from All Sources

Selection/reduction process	Original no. of articles	No. of articles remaining
Search through 15 data bases, pharmaceutical companies, and ESHRE	4 840	—
Duplicates or obvious false-positive hits	2 240	2 600
Articles unobtainable within constraints of study or source could not be located	949	1 651
Total no. reviewed	1 651	—
Reviewed but did not meet inclusion criteria	714	937
Total no. of articles coded and analyzed	937	—

With respect to the attempt to obtain unpublished or non-peer-reviewed literature, all of the selected pharmaceutical companies responded to the request for such material. However, most of the information received by the investigators was the same as that available publicly through electronic data bases. Little, if any, new information based on the results of in-house studies was reported.

Of the 58 articles requested from the seventh meeting of the ESHRE and the seventh World Congress on *In Vitro* Fertilization and Assisted Procreation, eight papers were obtained from the ESHRE meeting, four of which met the selection criteria and were included in the coding and analysis process.

Adverse Outcomes of Ovulation Induction

Some of the manuscripts obtained through the literature search are listed in the bibliography. (The complete bibliography compiled from the literature search is available from the Commission's archives.) All of these documents were reviewed and, if an adverse outcome was indicated on the adverse outcomes sheet (Appendix 3), detailed coding was undertaken in accordance with the coding sheet.

The adverse effects of ovulation induction in women are presented in this report in several styles and sections. The crude rates, case reports, and reviews of outcomes per reviewed manuscript make up the bulk of the results and are presented in tabular form in an appendix (available from the Commission's archives). Each article in the summary tables is divided into specific adverse outcomes (Appendix 3) and contains only human data. Information such as the reference number, the effect size, the number of subjects, the design of the study, and the type of drug is documented for

each article. The pre-treatment code provides information concerning the indication for treatment and the specific type of effect size that could be ascertained for each adverse outcome. Significance (sign) and strength were recorded if there was a reported comparison. The year of publication, journal, and specific drug or drugs administered were also recorded. It was observed that there is a tendency for adverse outcomes to be reported without reference to a control group; few randomized controlled clinical trials have been conducted in this field. Further analyses of the data contained in the summary tables of adverse outcomes by article and animal study data are presented in Tables 2 to 11 and Figures 1 to 12.

Formal Meta-Analysis

Among the many adverse outcomes under review, only three were appropriate for formal meta-analysis. The specific topics analyzed were NTDs, congenital malformations, and alterations in the sex ratio of children. These outcomes were chosen because there were sufficient numbers of studies and adequate control populations. In addition, the subjects were highly relevant as they were directed into different qualitative outcomes. The study of NTDs and congenital malformations permits a review of the teratology of ovulation induction.

Neural Tube Defects

The results of the case-control and prospective studies that investigated the relationship between exposure to ovulation-inducing drugs before conception and NTDs are reported in Tables 2 to 5. The results of the prospective cohort investigation involving the assessment of periconceptual exposure to clomiphene in over 22 000 women indicated an elevated, but not significant, relative risk of NTDs in the exposed group (Milunsky et al. 1990).

Four out of the five case-control studies that were included in the meta-analysis reported odds ratios in excess of one. The estimate of the combined odds ratio across all five studies of 1.86 was significant ($p < 0.05$). This result suggests a slightly increased risk of NTDs when associated with ovulation induction. It is important to note the small sample size in most of the studies, because the addition or deletion of a single study can alter the significance of a positive result; a positive association between ovulation induction and NTDs is not conclusive evidence for a cause-and-effect relationship. Many other factors may come into play, such as the underlying cause of infertility, certain disease states, and possible geographic and environmental factors.

Congenital Malformations

The results of the meta-analysis do not provide evidence that a link exists between the use of clomiphene or hMG for ovulation induction and the occurrence of congenital malformations. When the articles are reviewed individually, some studies suggest a slightly increased risk of malformation.

However, when the articles are combined, this effect is not significant. Detailed information on the meta-analysis conducted on congenital malformations is presented in Tables 4 and 5.

Sex Ratio

The meta-analysis on sex ratio (Tables 6 and 7) suggests that there is a change in the sex ratio favouring more girls than boys for all births when all methods of ovulation induction are combined. Specifically, the use of clomiphene as an administered ovulation-inducing drug suggests a higher ratio of girls per boy for all births (94.2 boys per 100 girls) and for singleton births (79.0 boys per 100 girls). It should be noted that this includes one study in which hMG was also administered and two studies in which births were from therapeutic donor insemination.

The combined results for hMG exposure are inconsistent, with a reduced sex ratio in all births, singletons, and twins, but an increased ratio in higher multiples. Only the change in sex ratio for twins was significant (71.2 boys per 100 girls).

There were no IVF/gamete intrafallopian transfer studies in which the reported sex ratio differed significantly from the normal 106 boys per 100 girls. For donor insemination on the basis of two studies (one significant), there was an indication that the sex ratio was reduced, although all subjects also received clomiphene. A large study conducted in the United States reported a highly significant reduction in the sex ratio as a result of exposure to clomiphene and hMG. Similarly, a study in Israel also reported a significant reduction in the sex ratio associated with exposure to ovulation-inducing agents.

A change in the sex ratio may reveal differential toxicity, which occurs when the reproductive system is exposed to agents that stimulate ovulation. For example, it has recently been reported that a greater proportion of male embryos first attain the blastocyst stage (Tsumoda et al. 1985; Avery et al. 1989, 1991, 1992; Xu et al. 1991). A drug that alters the sex ratio may affect this result if there is a shortened time span for implantation that permits fewer male embryos to implant.

Combined Crude Rates

The combined crude rate deals with the integration of the crude adverse effects as determined by the initial review process. For each manuscript entered and by the adverse outcome of interest, the crude effect sizes from specific studies were combined. In addition to combining crude rates, four specific methods of reporting the effect sizes were used. These effect sizes are readily interpreted by patient and physician alike. They refer to the crude rate in percent, the crude proportional difference between two groups in percent, the crude proportional difference in percentage of pregnancies obtained, and the crude proportional difference in percentage of live births obtained.

Crude proportional differences are the results obtained in two specific groups and the difference in specific outcomes between those two groups. The two groups may differ by treatment method, administered drug type or amount, control or treatment selection, or disease states. The results indicated are usually based on calculations of each case. An additional crude rate calculation is based on cycles of treatment. Table 8 is a summary of the adverse outcomes of most concern when clomiphene or hMG is administered for ovulation induction. The crude rates of adverse outcomes are presented in Tables 9 and 10.

Significant among the observations is the difference in effect sizes in relation to the total population of subjects under study. Clearly, small sample sizes of one study should not engender confidence.

In terms of the frequency of specific reproductive events, particularly spontaneous abortion, multiple pregnancy, and the individual types of multiple pregnancies, clomiphene appears to be less severe than hMG.

Heterotopic Pregnancy

The common occurrence of heterotopic pregnancy is relevant. This condition usually appeared as a single case report in association with misdiagnosis and complications such as haemoperitoneum due to rupture of a tubal ectopic pregnancy. Recognition of the relatively common occurrence of this condition by both medical staff and patients appears warranted. Traditionally, the rate was based on a calculation of the frequency of twins and ectopic pregnancy (approximately 1 in 30 000). All reports have indicated that this rate does not capture the impact of ovulation induction and new reproductive technologies in augmenting this rate.

Cancer

Very few reports were obtained that dealt with the development of cancer, particularly ovarian cancer. Therefore, a review of the IVF clinics in Canada was undertaken to capture any surplus case reports; three reports were obtained and two more were provided anecdotally. Of the three patients, ovarian cancer developed in two after treatment with ovulation induction therapy for one and five years, respectively. The other patient was found to have a tumour of low malignant potential in both ovaries at different times; an attempt was made to preserve reproduction before definitive therapy, at which time metastatic carcinoma was found.

In addition, the authors of several large epidemiologic studies of ovarian cancer were contacted directly because of a possible identified association between infertility and ovarian cancer. However, records had not been kept consistently on drugs used for ovulation induction among those identified as infertile; thus, an association between ovulation-inducing drugs and cancer could not be determined.

These findings do not exclude a relationship between ovulation induction and ovarian cancer. Many issues must be considered, including susceptibility, temporal delay of exposure to presentation, and the

possibility that such drugs may stimulate an existing cancer and subsequently interfere with prognosis.

Animal Studies Review

The effects of ovulation induction in various animal species are presented in an annotated bibliographic form (see Table 11). The review covers clomiphene citrate, adverse outcomes in relation to the year of publication, species, design of study, total number of animals in the experiment, degree of significance, and uncollated effect size.

The number of animal studies that examine the adverse effects of hMG or FSH is small; thus, Table 11 contains little information on these two drugs. Pregnant mare serum gonadotropin (PMSG) is often used in animal studies as a substitute for hMG. However, most of the literature that relates to PMSG does not specifically examine its adverse effects but rather its physiologic actions in producing desired effects or outcomes. In Table 11, the outcomes related to PMSG can be compared with the effects of hMG.

Because of the broad experimental design of individual studies, it is difficult to combine or group studies into specific adverse outcomes.

The results of the studies reveal that clomiphene has severe effects when used in respect of reproductive performance in animals; most indicate an adverse outcome. Specifically, in the female, reports indicate alterations in the ovary (weight suppression), oocyte (chromosomal abnormalities), early embryo (chromosomal abnormalities), uterine cavity (reduced embryonic implantation), and neonatal genital tract (induction of heterotopic epithelium when neonatal animals are treated). Due to the severity of the effects observed in animals, the impact on humans is of concern.

Among this list of phenomena, the actual mechanisms of action are not understood. Although many can be explained by the similarity of clomiphene to estrogen activity, particularly in the neonatal mouse and rat, others defy current understanding. For example, why do oocytes obtained from an ovary perfused *in vitro*, inseminated, and administered to a host animal fail to implant? Implantation appears to be particularly vulnerable in certain animal species exposed to these drugs. The long-observed and poorly understood differentiation between ovulation rate and pregnancy rate among women treated with clomiphene may be similar to the outcomes of oocytes derived from perfused rabbit ovaries (Yoshimura et al. 1988).

The traditional means of extrapolating animal information to humans, using a risk assessment model, is to determine that an agent is a hazard, define the dosage at which there is no effect, and apply a safety factor. This process is based on the supposition that animals are more susceptible to toxicants than humans; however, this may not be so, and significant challenges have been made regarding this concept, particularly from the perspective of germ cell destruction.

Presented with the broad array of reported adverse outcomes in so many animal species studies, the origin of the use of clomiphene as an inducer of ovulation is of interest. From the literature it seems that early clinical trials were conducted on the basis of the ability of the drug to induce ovulation in animals made anovulatory by steroid treatment of central nervous system lesions. Clearly, in the intact animal the agent acts as a contraceptive.

In formulating recommendations on the use of clomiphene in humans based on the findings of this literature search, two major issues are evident. First, there is a need for continued monitoring of adverse effects in a more robust manner. In particular, the potential activity of the agent in early pregnancy to alter embryonic genital tract epithelium has not been resolved completely and, at the least, a case-control study of women who were exposed to clomiphene as a fetus would be appropriate. Second, because so many of the animal studies have reported adverse outcomes that are poorly understood, it is appropriate that some discussion should be part of informed consent before administration.

Canadian Infertility Clinic Survey: Adverse Outcomes

A total of 28 fertility clinics across Canada responded to the questionnaire on ovulation induction, a response rate of approximately 60%. Reported adverse health effects related to the administration of clomiphene, hMG, or both are presented in Figures 1 to 12.

Outcomes that underwent formal meta-analysis or combined crude rate analysis during the literature review process were compared with the perceived or documented outcomes as reported by the clinics.

Variations in the estimated occurrence of adverse outcomes were reported, with most clinics reporting a perceived percentage of occurrence similar to the rate calculated through formal meta-analysis or combined crude rate analysis. Two clinics reported a total of five cases of ovarian cancer, two of which were anecdotal. The clinical information obtained from these case reports does not prove or disprove that clomiphene or hMG treatments for ovulation induction are related to ovarian cancer.

Figures 1 and 2 indicate crude estimates of the number of patients per clinic and the frequency of clomiphene and hMG administration.

The perceived occurrence of multiple pregnancy, congenital malformations, hyperstimulation, ovarian pain, and ovarian cysts corresponds with the results obtained from the literature review process. However, the estimated number of pregnancies and spontaneous abortions in patients receiving clomiphene or hMG deviates from that reported in the literature. Three-quarters of the clinics (18 of 24) perceive the rate of spontaneous abortion due to hMG treatment to be lower than that reported by the combined crude rate analysis. Similarly, the clinics perceived the pregnancy rate due to treatment as somewhat greater than that in the reported literature. The estimation of pregnancy rates for clomiphene and hMG is

scattered, ranging from 10% to 80%. The estimation of pregnancy rates as indicated in the reviewed literature suggests a success rate of 30% to 40%.

Table 2. Case-Control Studies of Neural Tube Defects — Combined Studies

	Ovulation induction		Spontaneous ovulation		Odds ratio (95% CI)
Study	NTDs	Normal	NTDs	Normal	Normal
Mills et al. (1990)	8	10	563	563	0.80 (0.3-2.3)
Cornel et al. (1989)	3	8	91	962	3.96 (1.0-15.2)
Robert et al. (1991)	11	114	169	4 133	2.36 (1.2-4.5)
Czeizel (1989)	3	12	822	18 892	5.75 (1.6-20.4)
Cuckle and Wald (1989)	4	5	103	209	1.62 (0.4-6.2)
Combined	29	149	1 748	24 759	1.86[1] (1.2-2.9)

[1] For these studies, the combined estimate of the common odds ratio (Mantel-Haenszel) was calculated using a Minitab Data Analysis software macro program. A logistic regression model was used to assess the interaction of exposure to ovulation induction and study. This interaction was not significant (p = 0.13); there was no evidence of heterogeneity of the odds ratios across the studies. The combined odds ratio estimate and 95% CI from the logistic regression model was 2.0 (1.2-3.3).

Table 3. Ovulation Induction and Neural Tube Defects: Results from Case-Control and Cohort Studies Not Included in the Meta-Analysis

Case-control study

Mili et al. (1991a)

- There was no association between the maternal use of clomiphene citrate and NTDs (n = 345, odds ratio = 1.1). Insufficient data to include in the meta-analysis.

Prospective cohort investigation

Milunsky et al. (1990)

• Clomiphene exposure during three months prior to pregnancy.		• No clomiphene exposure during three months prior to pregnancy.		
NTDs	Normal	NTDs	Normal	Risk ratio (RR) (95% CI)
2	436	47	22 317	2.2 (0.6-8.6)

Table 4. Combined Rates of Neural Tube Defects and Congenital Anomalies with 95% Confidence Intervals[1]

Treatment	(No. of studies)	Drugs	Births	NTDs			CM++			Probability of expected no.[2]	
				No.	Rate	95% CI	No.	Rate	95% CI	NTDs	CM
IVF*	(6)	42	1 835	5	0.27	0.09-0.62				n.s.‡	
	(7)	42	6 430				145	2.26	1.9-2.70		n.s.
IVF/GIFT**	(10)	42	11 997	34	0.28	0.24-0.40				n.s.	
	(11)	42	12 963				277	2.14	1.9-2.40		n.s.
CC+	(13)	1	2 512	6	0.24	0.09-0.51				n.s.	
	(16)	1	7 659				167	2.18	1.9-2.50		n.s.
All	(31)	1,2,10	15 857	420	2.65	0.19-0.36				n.s.	
	(36)	1,2,10	22 257				480	2.16	2.0-2.40		n.s.
All (no IVF/GIFT)	(21)	1,2,10	3 860	8	0.21	0.09-0.40				n.s.	
	(25)	1,2,10	9 294				203	2.18	1.9-2.50		n.s.
hMG/hCG	(5)	2,10	791	2	0.25	0.03-0.87	17	2.15	1.3-3.44	n.s.	n.s.

* *In vitro* fertilization
** Gamete intrafallopian transfer
\+ Clomiphene citrate
++ Congenital malformation
‡ Not significant

[1] 95% CIs calculated according to the formula provided by Ury and Wiggins (1985).
[2] Based on the average population rates reported in the studies included in the analysis.

Table 5. Neural Tube Defects and Congenital Malformations for Individual Studies

Treatment	Author(s)	Country	Drugs	Births/ stillbirths
IVF/GIFT	MRC (1990)	U.K.	42	1 581
	Lancaster (1987)	Aust.	42	1 694
	MRI (1989)	U.S.	42	1 871
	Lancaster et al. (1991)	Aust./N.Z.	1,2	5 016
IVF only	Australian IVF Group (1985)	Aust.	42	186[4]
	Andrews et al. (1986)	U.S.	42	115
	Saunders et al. (1988)	Aust.	42	1 094
	Lancaster et al. (1991)	Aust./N.Z.	42	3 629[5]
	Seoud et al. (1991)	U.S.	42	98[8]
	Karabacak et al. (1989)	Turkey	42	128[9]
	Cohen et al. (1988)	France	42	1 195
	Barjot et al. (1991)	France	42	113[9]
GIFT only	Lancaster et al. (1991)	Aust./N.Z.	42	1 387[5]
hMG/hCG	Samberg et al. (1983)	Israel	2,10	23[4]
	Kurachi et al. (1985)	Japan	2,10	509
	Caspi et al. (1976)	Israel	2,10	157
	Tyler (1968)	U.S.	2	36
	Harlap (1976)	Israel	2	66
	Kurachi et al. (1983)	Japan	2,10	213
Clomiphene	Kurachi et al. (1983)	Japan	1	935
	Ahlgren et al. (1976)	Sweden	1	148
	Lee et al. (1982)	Canada	1	25[4]
	Goldfarb et al. (1968)	U.S.	1	183[11]
	Gysler et al. (1982)	U.S.	1	155[13]
	Correy et al. (1982)	Aust.	1	137
	Merrion Merrell Dow (1991)	U.S.	1	2 369[9]

NTDs*		CM**		Population rates†		Probability of observed no.††	
No.	Rate	No.	Rate	NTDs	CM	NTDs	CM
10	0.63	35	2.21	0.360[1‡‡]	2.00[1‡‡]	n.s.	n.s.
6[2]	0.35	37	2.18	0.070[2]	n.r.	0.0015[3]	n.s.‡
4	0.21	16	0.86	n.r.	n.r.	n.s.‡	n.s.‡
9[1]	0.18	n.r.	n.r.	0.070[1‡‡]	n.r.	< 0.0500[5]	n.a.
0	0.00	2	1.08	n.r.	n.r.	n.s.‡	n.s.‡
1	0.87	3	2.61	n.r.	2.70	n.s.‡	n.s.
n.r.	n.r.	23	2.10	n.r.	1.50	n.a.	> 0.05
n.r.	n.r.	77	2.12	n.r.	n.r.	n.a.	n.s.‡
0[7]	0.00	0	0.00	n.r.	n.r.	n.s.‡	n.s.‡
1	0.78	n.r.	n.r.	0.226	n.r.	n.s.	n.a.
3	0.25	33	2.76	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	7[10]	6.19	n.r.	3.00	n.s.‡	n.s.
n.r.	n.r.	44	3.17	n.r.	n.r.	n.a.	n.s.‡
0	0.00	2	8.70	n.r.	2.90[12]	n.s.‡	n.s.
2	0.39	9	1.77	n.r.	1.70	n.s.‡	n.s.
0	0.00	4	2.55	n.r.	1.00[12]	n.s.‡	n.s.
0	0.00	1	2.78	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	1	1.52	n.r.	1.03	n.s.‡	n.s.
0	0.00	3	1.41	0.270	1.70	n.s	n.s.
2	0.21	9	0.96	0.270	1.70	n.s.	n.s.[6]
1	0.68	8	5.41	n.r.	3.20	n.s.‡	n.s.[6]
0	0.00	2	8.00	n.r.	6.50	n.s.‡	n.s.
1	0.55	2	1.09	n.r.	n.r.	n.s.‡	n.s.[6]
0	0.00	4	2.58	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	5	3.65	n.r.	1.40	n.a.‡	0.04
n.r.	n.r.	58	2.45	n.r.	n.r.	n.a.	n.s.‡

Table 5. (*cont'd*)

Treatment	Author(s)	Country	Drugs	Births/ stillbirths
Clomiphene (*cont'd*)	Merrion Merrell Dow (1991)	U.S.	1	158[9,15]
	Kistner (1965)	U.S.	1	38[15]
	Kistner (1965)	U.S.	1	300[9]
	Adashi et al. (1979)	U.S.	1	64
	Aono et al. (1983)	Japan	1	1 034
	Holmes et al. (1982)	U.S.	1	40
	Harlap (1976)	Israel	1	225
	Hack et al. (1972)	Israel	1	104
	Varma et al. (1988)	U.S.	1	347[14]
	MacGregor et al. (1968)	U.S.	1	1 744
Induction not specified or combination	Hack et al. (1970)	Israel	42	122
	Ferrier et al. (1982)	Switzerland	42	222
	Thompson & Hansen (1970)	U.S.	1,2,10	287[9,13]

* Excluding hydrocephalus; including spina bifida, anencephaly, encephalocele, iniencephaly, meningocele, myelomingocele — rates in %

** Major malformations detectable at birth, including chromosomal anomalies and associated syndromes — rates in %

\+ Based on the population reported by the authors — rates in %

\+\+ Probability of obtaining the observed proportion of NTDs or CM based on the binomial distribution using the population value reported by the authors as the expected probability of occurrence of an adverse event

‡ Probability based on the average of population rates reported in all studies, unless otherwise specified (average rate of NTD is 0.28%; malformation rate is 2.3%)

‡‡ Extrapolated from the expected number

n.r., not reported; n.a., not applicable; n.s., not significant.

[1] Average of two population rates adjusted for maternal age.

[2] All cases had spina bifida, rate applies for spina bifida only.

NTDs*		CM**		Population rates†		Probability of observed no.††	
No.	Rate	No.	Rate	NTDs	CM	NTDs	CM
1	0.63	8	5.06	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	1	2.63	n.r.	n.r.	n.s.‡	n.s.‡
1	0.33	3	1.00	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	2	3.13	n.r.	n.r.	n.s.‡	n.s.‡
n.r	n.r	23	2.22	n.r.	1.70	n.a.	n.s.
0	0.00	0	0.00	n.r.	3.60	n.s.‡	n.s.
0	0.00	2	0.89	n.r.	1.03	n.s.‡	n.s.[6]
0	0.00	2	1.92	n.r.	1.27	n.s.‡	n.s.[6]
1	0.29	2	0.58	n.r.	3.80	n.a.	n.a.
n.r.	n.r.	38	2.18	n.r.	n.r.	n.a.	n.a.
0	0.00	4	3.28	n.r.	n.r.	n.s.‡	n.s.‡
0	0.00	7	3.15	n.r.	n.r.	n.s.‡	n.s.‡
n.r.	n.r.	5	1.74	n.r.	n.r.	n.a.	n.s.[6]

[3] One-sided Poisson reported by authors.
[4] Live births only.
[5] Live births, stillbirths, and induced abortions.
[6] Reported by the authors.
[7] Inguinal hernia and macroglossia excluded.
[8] Triplets and quadruplets only.
[9] Number of pregnancies.
[10] Includes four pregnancies terminated therapeutically due to presence of malformations.
[11] Pooled data from case reports and case series.
[12] Average of more than one population rate reported.
[13] Excludes one neonatal death due to multiple anomalies in which types were not reported.
[14] Women exposed to clomiphene — data not included in combined results.
[15] Exposure during pregnancy only.

Table 6. Sex Ratios Combined

Treatment/type of birth	Births	Singletons M	Singletons F	Twins M	Twins F	Triplets or higher M	Triplets or higher F	All M	All F	Sex ratio*	z
IVF/GIFT											
All births	4 194							2 142	2 052	104.4	–0.55
Singletons	1 680	859	821							104.6	–0.30
Twins	498			255	243					104.9	–0.13
Triplets or higher	154					85	69			123.2	0.92
Clomiphene[3]											
All births	2 414							1 171	1 243	94.2	–2.94[2]
Singletons	222	98	124							79.0	–2.19[1]
Twins	125			55	70					78.6	–1.68
Triplets or higher	103					49	54			90.7	–0.80
hMG/hCG											
All births	423							202	221	91.4	–1.54

Twins	125			52	73					71.2	−2.21[1]
Triplets or higher	63					38	25			152.0	1.40
Induction not specified (Hack et al. 1970)											
All births	115							47	68	69.1	−2.28[1]
Singletons	47	22	25							88.0	−0.64
Twins	46			14	32					43.8	−2.86[2]
Triplets or higher	22					11	11			100.0	−0.14
All results combined											
All births	7 146							3 562	3 584	99.4	−2.80[2]
Singletons	2 175	1 090	1 085							100.5	−1.29
Twins	794			376	418					90.0	−2.34[1]
Triplets or higher	342					183	159			115.1	0.74

* Number of males per 100 females.

Notes: Significant at $p < 0.05$ (two-sided). Significant at $p < 0.01$ (two-sided). Includes one study in which hMG and hCG were administered and two studies in which all births were from therapeutic donor insemination.

Table 7. Sex Ratios for Individual Studies

Treatment/ author(s)	Country	Drugs	Births	Singletons		Twins		Triplets or higher		All		Sex ratio*	z
				M	F	M	F	M	F	M	F		
IVF/GIFT													
MRC (1990)	U.K.	42	1 388	432	411	210	202	76	57	718	670	107.2	0.17
Australian IVF Group (1985)	Aust.	42	186	55	59	30	24	7	11	92	94	97.9	−0.56
MRI (1989)	U.S.	42	1 637	n.r.**	n.r.	n.r.	n.r.	n.r.	n.r.	805	832	96.8	−1.88
Andrews et al. (1986)	U.S.	42	115	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	64	51	125.5	0.89
Seoud et al. (1991)	U.S.	42	700	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	384	316	121.5	1.78
Cohen et al. (1988)	France	42	590[4]	310	280	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	110.7	0.51
Edwards (1985)	U.K.	42	168	62	71	15	17	2	1	79	89	88.8	−1.16
Donor insemination													
Sampson et al. (1983)	U.S.	1	111	41	48	15	7	0	0	56	55	101.8	−0.22
Mason (1984)	U.K.	1	809	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	385	424	90.8	−2.22[1]
CC induction													
Lee et al. (1982)	Canada	1	20	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	10	10	100.0	−0.13
Correy et al. (1982)	Aust.	1	132	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	73	59	123.7	0.87
Adashi et al. (1979)	U.S.	1	100	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	58	42	138.1	1.30
Hack et al. (1972)	Israel	1	88	n.r.	n.r.	8	8	n.r.	n.r.	48	40	120.0	0.57
Potashnik et al. (1983)	Israel	1	22	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	5	17	29.4	−2.70[2]

Huuskonen (1985)	Finland	1	89	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	41	48	85.4	−1.02
Black et al. (1969)	Aust.	1	32	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	19	13	146.2	0.89
Shimizu et al. (1978)	Japan	1	226	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	126	100	126.0	1.28
Zourlas & Hassiakos (1984)	Greece	1	99	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	53	46	115.2	0.40
Shettles (1984)	U.S.	1	39	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	13	26	50.0	−2.26[1]
Senez & Gillet (1978)	France	1,10	57	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	27	30	90.0	−0.62
hMG/hCG													
Caspi et al. (1976)	Israel	2,10	151	32	50	18	23	19	9	69	82	84.1	−1.50
Ben-Rafael et al. (1986)	Israel	2,10	256	79	65	34	50	15	13	128	128	100.0	−0.48
Burnell (1974)	U.S.	2,10	n.r.	n.r.	n.r.	n.r.	n.r.	4	3	n.r.	n.r.	133.3	0.30
Zourlas and Mantzavinos (1980)	Greece	2	15	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	5	10	50.0	−1.41
CC/hMG													
James (1980)[5]	U.S.	1,2,10	590	57	76	32	55	49	54	257	333	74.6	−3.86[3]
Induction not specified													
Hack et al. (1970)	Israel	42	115	22	25	14	32	11	11	47	68	69.1	−2.28[1]

* Number of males per 100 females.
** Not reported.

Notes: Significant at $p < 0.05$ (two-sided). Significant at $p < 0.01$ (two-sided). Significant at $p < 0.001$ (two-sided). Singletons only. Not all cases of singletons, twins, and triplets or higher are included in the figures presented here — thus, the differences in the totals.

Table 8. Combined Crude Rates of Adverse Outcomes of Ovulation Induction for Clomiphene Citrate and Human Menopausal Gonadotropin

	Clomiphene citrate			hMG*		
Outcome	%	No. of studies	No. of patients	%	No. of studies	No. of patients
Combined crude rates						
Hyperstimulation	8.20	1	29/354	7.30	19	1 171/16 103
Abortion	21.60	35	3 550/17 202	25.90	100	8 175/31 618
Ectopic	1.60	4	98/6 225	3.30	37	678/20 624
Stillbirth	1.70	4	55/3 298	6.30	6	64/1 010
Multiple pregnancy	7.90	16	966/12 250	20.75	45	1 783/8 593
Twins	6.50	12	321/4 920	12.70	45	2 318/18 248
Triplets	0.66	4	21/3 158	2.30	29	336/14 710
Quadruplets	0.31	3	14/4 499	0.65	9	76/11 653
Quintuplets	0.11	1	3/2 635	0.51	3	6/1 186
Prematurity	5.10	8	388/7 560	11.80	14	299/2 528
Heterotopic	0.93	1	1/108	2.90	9	38/1 311
Meta-analysis						
Change in sex ratio	94.2 men / 100 women, $p < 0.05$			Not significant		
Congenital malformations	Not significant			Not significant		
Neural tube defects	Odds ratio = 1.86 95% confidence interval (1.2-2.9)**					

* hMG includes all associated treatments except clomiphene citrate.

** Reported rate includes clomiphene, hMG, and other drugs used for ovulation induction.

Table 9. Adverse Outcomes Attributable to Clomiphene Citrate Reported by Case

Adverse outcome	Crude rate				Crude proportion per cycle				Crude proportion per pregnancy			
	No. SA*	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST
Gastrointestinal												
Abdominal pain	6.00	152	3.9	2	—	—	—	—	—	—	—	—
Nausea/vomiting	133.00	6 044	2.2	5	—	—	—	—	—	—	—	—
Anorexia	34.00	53	64.2	2	—	—	—	—	—	—	—	—
Bloating/pain	7.00	146	4.8	1	—	—	—	—	—	—	—	—
Nervous system												
Dizziness	5.00	156	3.2	3	—	—	—	—	—	—	—	—
Insomnia	1.02	102	1.0	1	—	—	—	—	—	—	—	—
Depression	11.00	544	2.0	3	—	—	—	—	—	—	—	—
Headache	3.00	201	1.5	2	—	—	—	—	—	—	—	—
Hyperexcitability	1.00	37	2.7	1	—	—	—	—	—	—	—	—
Skin												
Bullae/urticaria dermatitis	1.00	28	3.6	1	—	—	—	—	—	—	—	—
Special senses												
Blurred vision	2.00	35	5.7	1	—	—	—	—	—	—	—	—
Visual effects, not otherwise classified	115.00	6 514	1.8	6	—	—	—	—	—	—	—	—

Table 9. (*cont'd*)

Adverse outcome	Crude rate				Crude proportion per cycle				Crude proportion per pregnancy			
	No. SA*	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST
Urogenital — female												
Ovarian enlargement	1 582.00	11 671	13.6	16	—	—	—	—	—	—	—	—
Hyperstimulation	29.00	354	8.2	4	4.08	680	0.6	1	—	—	—	—
Pelvic pain	18.00	108	16.7	4	—	—	—	—	—	—	—	—
Ovarian cysts	47.00	350	13.4	6	—	—	—	—	—	—	—	—
Change endometrium maturation	136.00	414	32.9	1	—	—	—	—	—	—	—	—
Ovarian torsion	0.99	22	4.5	1	—	—	—	—	—	—	—	—
Breast pain	116.70	5 836	2.0	1	—	—	—	—	—	—	—	—
Second generation												
Cleft lip/palate	—	—	—	—	—	—	—	—	2.67	62	4.3	1
Cardiovascular	—	—	—	—	—	—	—	—	2.89	289	1.0	1
Perinatal mortality	—	—	—	—	—	—	—	—	5.57	159	3.5	1
Minor malformation	—	—	—	—	—	—	—	—	33.50	347	9.7	2
Abnormal digits	—	—	—	—	—	—	—	—	2.89	289	1.0	1
Testes undescended	44.30	1 704	2.6	1	—	—	—	—	—	—	—	—

* Reported by cycle.
SA, subjects affected; S, subjects; CR, crude rate; ST, studies.

Table 10. Adverse Outcomes Attributable to Human Menopausal Gonadotropin Combined with All Other Drugs Except Clomiphene Citrate by Case

	Crude rate				Crude proportion per cycle				Crude proportion per pregnancy				Crude proportion per live birth			
Adverse outcome	No. SA*	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST
Gastrointestinal	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Abdominal pain	2 368	2 553	92.8	1	—	—	—	—	—	—	—	—	—	—	—	—
Nausea/ vomiting	38	335	11.3	2	—	—	—	—	—	—	—	—	—	—	—	—
Anorexia	1 251	2 553	49.0	1	—	—	—	—	—	—	—	—	—	—	—	—
Nervous system																
Pulmonary distress	511	2 553	20.0	1	—	—	—	—	—	—	—	—	—	—	—	—
Headache	95	314	30.3	2	—	—	—	—	—	—	—	—	—	—	—	—
Fatigue	84	158	53.2	1	—	—	—	—	—	—	—	—	—	—	—	—
Urogenital — female																
Ovarian enlargement	10	302	3.3	2	18	279	6.5	2	—	—	—	—	—	—	—	—

Table 10. *(cont'd)*

Adverse outcome	Crude rate				Crude proportion per cycle				Crude proportion per pregnancy				Crude proportion per live birth			
	No. SA*	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST
Hyper-stimulation	363	4 109	8.8	23	9	296	3.0	23	35.0	444	7.9	4	—	—	—	—
syndrome	20	652	3.1	1*	1 171	16 103	7.3	19*	37.0	301	12.3	2	—	—	—	—
Pelvic pain	1	101	1.0	1	—	—	—	—	—	—	—	—	—	—	—	—
Ovarian cysts	54	207	26.1	3	—	—	—	—	8.1	177	4.6	1*	—	—	—	—
Ovarian	4	648	0.6	1	—	—	—	—	—	—	—	—	—	—	—	—
Breast tenderness	116	5 836	2.0	1	—	—	—	—	—	—	—	—	—	—	—	—
Pregnancy																
Multiple births, not otherwise classified	2 736	16 557	16.5	4	267	850	31.4	2*	1 783.0	8 593	20.7	45	6 311	31 407	20.1	17
Premature birth	4	20	20.0	1	—	—	—	—	—	—	—	—	—	—	—	—
	—	—	—	—	—	—	—	—	299.0	2 528	11.8	14	—	—	—	—
	—	—	—	—	—	—	—	—	171.0	977	17.5	3*	—	—	—	—
Abortion	4 242	16 790	25.3	8	136	850	16.0	2*	8 175.0	31 618	25.9	100	8	66	12.1	2
	—	—	—	—	—	—	—	—	8 161.0	38 697	21.1	45*	8	210	3.8	1*

	—	—	—	—	—	—	—	—	1 505.0	27 458	5.5	16	—	—	—	—
Stillbirth	—	—	—	—	—	—	—	—	64.0	1 010	6.3	6	49	2 329	2.1	1
	—	—	—	—	—	—	—	—	101.0	373	27.1	1*	—	—	—	—
Caesarian	—	—	—	—	—	—	—	—	552.0	10 290	5.4	7	1 344	2 820	47.7	4
Hyper-tension	—	—	—	—	—	—	—	—	12.2	36	33.9	2	—	—	—	—
Intrauterine growth retardation	—	—	—	—	—	—	—	—	2.0	31	6.5	1	—	—	—	—
Molar	—	—	—	—	—	—	—	—	1.0	143	0.7	1	—	—	—	—
	—	—	—	—	—	—	—	—	5.0	661	0.8	1*	—	—	—	—
Toxaemia	—	—	—	—	—	—	—	—	35.0	492	7.1	3	—	—	—	—
Hetero-topic	—	—	—	—	—	—	—	—	38.5	1 311	2.9	9	—	—	—	—
	—	—	—	—	—	—	—	—	44.2	2 072	2.1	5*	—	—	—	—
	—	—	—	—	—	—	—	—	2 318.0	18 248	12.7	45	414	2 454	16.9	2
	—	—	—	—	—	—	—	—	1 443.0	10 284	14.0	19*	—	—	—	—
Triplets	12	15	80.0	1	—	—	—	—	336.0	14 710	2.3	29	64	2 454	2.6	2
	—	—	—	—	—	—	—	—	296.0	6 738	4.4	13*	—	—	—	—

Table 10. (*cont'd*)

Adverse outcome	Crude rate				Crude proportion per cycle				Crude proportion per pregnancy				Crude proportion per live birth			
	No. SA*	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST	No. SA	No. S	CR (%)	No. ST
Quadruplets	—	—	—	—	—	—	—	—	75.50	11 653	0.6	9	—	—	—	—
	—	—	—	—	—	—	—	—	80.40	4 023	2.0	5*	—	—	—	—
Quintuplets	—	—	—	—	—	—	—	—	5.53	1 186	0.5	3	—	—	—	—
	—	—	—	—	—	—	—	—	12.13	3 152	0.4	2*	—	—	—	—
Selective abortion	—	—	—	—	—	—	—	—	1.70	852	0.2	1	—	—	—	—
Delay ectopic diagnosis	—	—	—	—	—	—	—	—	9.10	312	2.9	1	—	—	—	—
Miscellaneous																
Abdominal distension	85	314	27.1	1	—	—	—	—	—	—	—	—	—	—	—	—
Weight gain	160	314	51.0	2	—	—	—	—	—	—	—	—	—	—	—	—
In vitro fertilization																
Retarded blastocyst development	84	397	21.2	1	—	—	—	—	—	—	—	—	—	—	—	—
Abnormal chromosome																

chromosome embryo	45	159	28.3	2	—	—	—	—	—	—	—	—	—	—	—	—	
Cleavage rate quality	192	587	32.7	3	61.0	102	59.8	1	—	—	—	—	—	—	—	—	
Recovery of oocytes	—	—	—	—	3.7	64	5.8	1	—	—	—	—	—	—	—	—	

* Reported by cycle.
SA, subjects affected; S, subjects; CR, crude rate; ST, studies.

Table 11. Adverse Outcomes of Ovulation-Inducing Drugs Based on Animal Studies

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Thomson (1968)	retarded transformation to blastocyst	clomiphene	1968	mouse	*in vitro*		< 0.0010	41.7	clomiphene citrate (cc) prevents the development of early mouse embryo *in vitro*
Laufer et al. (1982)	degeneration of ova	clomiphene	1982	rat	*in vitro*	211	< 0.0010	35.0	cc decreased degeneration of ova when cultured with rat follicles
Chang (1964)	delayed oocyte maturation	clomiphene	1964	rabbit	*in vivo*			55.0	cc resulted in rapid transit of blastocysts into vagina and increased ova atresia rates

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Courtney & Valerio (1968)	stillbirth/neonatal death/fetus not viable	clomiphene	1968	monkey	*in vivo*	18		11.0	11% of pregnancies treated with cc resulted in stillbirth; no anomaly
	increased rate of malformation/ malformations, not otherwise classified	clomiphene	1968	monkey	*in vivo*			0.0	no increase in malformations noted
Diener & Hsu (1967)	increased rate of malformation/ malformations, not otherwise classified	clomiphene	1967	rat	*in vivo*	70	< 0.0500	8.4	cc given days 6-20 (to avoid implantation problems)
	abnormal bones	clomiphene	1967	rat	*in vivo*	70	< 0.0500	18.5	cc induced increased rate of bony malformations
	decreased rate of implantation/ inhibition of implantation	clomiphene	1967	rat	*in vivo*	70	< 0.0500	100.0	treated days 1-14 of pregnancy reduced implantations
Branham et al. (1988a)	decreased uterine weight	clomiphene	1988	rat	*in vivo*			100.0	cc is estrogenic to neonatal rat (uterine weight prior to puberty); cc alters uterine epithelium

et al. (1980)	hyperstimulation							ovaries not similar to humans
Forsberg (1985)	vaginal adenosis	clomiphene	1985	mouse	*in vivo*		100.0	heterotopic epithelium of ovaries and vagina in neonatally treated rats
Nakago et al. (1980)	vaginal adenosis	clomiphene	1980	rat	*in vivo*		60.0	heterotopic uterine epithelium in five-day-old rats receiving cc
	vaginal basal cell hyperplasia						20.0	vaginal basal cell hyperplasia
Fourie et al. (1987)	oocyte fertilization	Clomid®	1987	monkey			33.0	cc showed reduced fertilization and cleavage rates when compared with hMG in the monkey
		hMG					44.0	
	cleavage rate	Clomid®					3.2	
		hMG					14.8	
Takagi & Sasaki (1976)	increased rate of triploidy/ polypronuclear embryos	PMSG, hCG	1976	mouse	*in vivo*	1 827	16.3	superovulated mice were found to have higher rates of embryo heteroploidy
Kaufman (1973)	chromosomal abnormality in embryos	PMSG	1973	mouse	*in vivo*	1 766	12.4	incidence of anomalies of the one cell fertilized egg

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Vickers (1969)	chromosomal abnormality in embryos	PMSG	1969	mouse	*in vivo*	611		2.6	in superovulated mice delayed fertilization, increased embryos anomaly rate and chromo-somal abnormality rate, especially triploidy rate, which increased nine times Control Delay Delay 3-4 9-11 2.37% 3.86% 5.26%
Fujimoto et al. (1974)	chromosomal abnormality in embryos	PMSG	1974	rabbit	*in vivo*	15		9.7	PMSG induced a 9.7% increase in rate of abnormal blastocysts from rabbit uterus
Sengoku & Dukelow (1988)	chromosomal abnormality in embryos	PMSG	1988	hamster	*in vivo*				no effect of PMSG on chromosomes of hamster
Nelson et al. (1990)	decreased rate of implantation/ inhibition of implantation	clomiphene	1990	mouse	*in vivo*				

Taubert (1971)	of implantation/ inhibition of implantation								female rats
Schwantje & Taubert (1971)	increased ratio of corpora lutea	clomiphene	1971	rat	*in vivo*	24		47.0	cc induces ovulations in pseudopregnant rats
Pakrashi et al. (1969)	decreased rate of implantation/ inhibition of implantation	clomiphene	1969	mouse	*in vivo*	196	< 0.0500	100.0	cc 100% anti-fertility on days 1-14 of pregnancy as indicated by no implantation sites
Basu (1973)	decreased rate of implantation/ inhibition of implantation	clomiphene	1973	mouse	*in vivo*	~ 75	< 0.0500	100.0	cc showed a 100% anti-fertility effect only when given pre-implantation; had no effect when given post-implantation
Davidson et al. (1965b)	decreased rate of implantation/ inhibition of implantation	clomiphene	1965	rat	*in vivo*	73	< 0.0500	100.0	the interval in treatment effects on anti-fertility extends from two days pre-coital to eight days (reduced implantation); administration after implantation does not reduce implants
	decreased ratio of births/all births	clomiphene	1965	rat	*in vivo*	61	< 0.0500	82.0	there is an implantation reduction in live births

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Barnes & Meyer (1962)	increased rate of triploidy polypronuclear embryos	clomiphene	1962	rat	*in vivo*		< 0.0500	100.0	cc prevented implantation in animals treated from days 1 to 7 (day 1 = day of insemination)
Prasad et al. (1965)	decreased rate of implantation/ inhibition of implantation	clomiphene	1965	rat	*in vivo*	63		73.5	delayed implantation was induced by ovariectomy and progesterone after insemination; these animals were given cc days 9-16, which resulted in 74% implant failure; blastotoxic effect of Clomid®
Davidson et al. (1965a)	decreased rate of implantation/ inhibition of implantation	clomiphene	1965	rat	*in vivo*			100.0	cc treatment of lactating females showed reduced implants, which could be attributed to altered implantation, rapid transit portal cytolysis
Robinzon et al. (1984)	increased egg production	clomiphene	1984	turkey hen	*in vivo*	20	< 0.0010	2.3	cc increases egg production in

(1987)	production								for random bred #1 types
Lindsay & Robinson (1970)	anovulation	clomiphene	1970	ewe	*in vivo*	59	< 0.0500	40.9	cc induced anovulation in ewes
Sahu (1987)	anovulation	clomiphene	1987	rat	*in vivo*	61	< 0.0100	76.0	cc induced anovulation in rats — adult
	increased ratio of corpora lutea	clomiphene	1987	rat	*in vivo*	61	< 0.0500	3.5	cc decreased ratio of corpora lutea
	decreased rate of recovery of oocytes	clomiphene	1987	rat	*in vivo*	61	< 0.0500	2.9	cc decreased rates of oocyte recovery
Edirisinghe et al. (1986)	decreased rate of recovery of oocytes	hMG vs. FSH	1986	mouse	*in vivo*	136	< 0.0500		PMSG gives better oocyte recovery response than FSH, 454/32 vs. 77/15
Basu (1972b)	decreased rate of implantation/ inhibition of implantation	clomiphene	1972	mouse	*in vivo*	14	< 0.0500	100.0	cc reduces implantation in the mouse
Groot-Wassink et al. (1982)	decreased rate of implantation/ inhibition of implantation	clomiphene	1982	rat	*in vivo*	1 984	< 0.0500	100.0	cc on first or second or fourth to sixth days of pregnancy prevents induction; estrogen on fourth or sixth days allows implantation

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Motta & Hutchinson (1991)	decreased rate of implantation/ inhibition of implantation	clomiphene	1991	guinea pig	*in vivo*		< 0.0100	49.0	cc given to guinea pigs results in marked reduction in implantation rate
Nelson et al. (1990)	decreased rate of implantation/ inhibition of implantation	clomiphene	1990	mouse	*in vivo*	160	< 0.0010		cc has a direct effect on endometrial receptivity reducing implantation
Gupta et al. (1974)	spontaneous abortion and pregnancy loss, not otherwise classified	clomiphene	1974	rat	*in vivo* pregnancy			100.0	cc given to rats on days 12, 14, 16, and 18 of pregnancy produced complete resorption of fetuses; blocked by reserpine
Hashizume et al. (1976)	premature birth	clomiphene	1976	rat	*in vivo* pregnancy	52		88.0	cc given in late pregnancy initiated premature delivery
Docke (1969)	increased ratio of corpora lutea	clomiphene	1969	rat	*in vivo* newborn	35	< 0.0500	48.0	neonatal androgenization of rats responded to ovulation in 48%
						35	< 0.0100	73.3	continuous exposure to light
						22	< 0.0100	100.0	hypothalamic lesions

									ovulated in response to cc 20 µg/day for five days
Koch et al. (1971)	increased ratio of corpora lutea	clomiphene	1971	rat	*in vivo*	24	< 0.0500	4.25	small doses of cc (1-100 mg/kg) induced ovulation in promathazine-treated rats
Branham et al. (1988a)	delayed/deficient endometrial maturation	clomiphene	1988	rat	*in vivo*		< 0.0500	–6.1	anti-estrogen (cc) has an inhibition effect on uterine epithelial development in two glands and lumen but not in uterine stroma
Branham et al. (1988a)	uterine gland area maturation	clomiphene	1988	rat	*in vivo*			10.8	delayed uterine maturation in neonatally treated rats
Leavitt & Meismer (1968)	decreased ovarian weight	clomiphene	1968					5.25	neonatal treatment of rats with a produced persistent estrus, anovulation, decreased ovarian and uterine weight
	uterine hyperplasia	clomiphene						14.5	
Clark & Guthrie (1983)	uterine hyperplasia	clomiphene	1983	rat	*in vivo*	80		92.0	clomiphene has estrogen-like effect in the neonatal period as evidenced by uterine hyperplasia

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Clark & Guthrie (1983)	enlarged uterus	clomiphene	1983	rat	*in vivo*				cc is estrogenic in the neonatal rat as evidenced by uterine hypertrophy and early vaginal opening
Bedrak et al. (1983)	improved egg hatchability	clomiphene	1983	hen	*in vivo*	1 046 eggs		4.1	improvement in egg hatchability
	improved egg laying					209 hens	< 0.0500		improvement in egg laying in broody hens
Brown et al. (1991)	decreased ovarian weight	clomiphene	1991	rat	*in vivo*	20		3.2	cc increases uterine weight and decreases pituitary weight in ovariectomized rats
Kumar & Chandrasek-har (1980)	advanced spawning	clomiphene	1980	teleost	*in vivo*				cc advances spawning by four months in the teleost
Hart (1990)	decreased pituitary weight	clomiphene	1990	rat	*in vivo*		< 0.0010	4.45	cc induces rapid reduction in pituitary weight in the chronically estrogenized rat
Fitzpatrick et al. (1980)	unsuccessful mating	clomiphene	1980	rat	*in vivo*	28		100.0	adult females were treated with cc for five days post partum, 0% mated

(1982)	tract epithelium								abnormal vaginal epithelium in the mouse after neonatal cc treatment
Ohnishi et al. (1986)	DNA strand breaks	clomiphene	1986	*E. coli*	*in vitro*				clomiphene induces DNA strand breaks in all *E. coli* tested but no SOS changes were noted
Yogo et al. (1977)	resorption of pregnancy	clomiphene	1977	rat	*in vivo*			100.0	treatment days 7-9 of pregnancy induces pregnancy loss
Clitheroe et al. (1966)	decreased uterine cut	clomiphene	1966	mouse	*in vivo*	72	< 0.0100	10.7	cc induces increased uterine weight in ovariectomized mice
Gupta et al. (1974)	resorption of pregnancy	clomiphene	1974	rat	*in vivo*			100.0	cc induces resorption of fetuses in rat on days 12-18 of pregnancy
Morishita et al. (1979)	vaginal opening, permanent sterility	clomiphene	1979	rat	*in vivo*			100.0	clomiphene induced permanent sterility, anovulations, and precocious vaginal opening
Staples (1966)	implantation reduced	clomiphene	1966	rat	*in vivo*			100.0	day 1 treatment with cc prevented implantation;

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Staples (1966) (*cont'd*)									females treated with clomiphene cannot implant donor oocytes
Yoshimura et al. (1988)	decreased pregnancy rate	clomiphene	1988	rabbit	*in vitro*	161 ova	< 0.0125	29.0	cc perfused into rabbit ovaries and hCG resulted in oocytes that produced fewer offspring than control; this was reversible by treating with estrogen
Gupta et al. (1974)	fetal resorption	clomiphene	1974	rat	*in vivo*	14		100.0	cc had a 100% lethal effect on fetus when dams treated days 12, 14, 16, and 18 — they were completely resorbed leaving the placenta
Birkenfeld et al. (1985b)	abnormal tubal and uterine epithelium	clomiphene	1985	rabbit	*in vivo*				rabbits were gonadectomized and treated with clomiphene and found to have abnormal tubal and uterus epithelium (possible cause of ectopic and heterotopic

et al. (1966)	endometrial maturation							demonstrated ovarian atrophy, although in the dogs that were
	ovarian atrophy	clomiphene		dog	*in vivo*		100.0	similar to rats, the ovaries showed atrophy and appeared relatively inactive; there was evidence of continued follicular development but many of the follicles were atretic
Morris et al. (1967)	decreased rate of implantation/ inhibition of implantation	clomiphene	1967	rat	*in vitro*	50	100.0	complete prevention of implantation when treated from days 2 to 9 in pregnancy; slightly less effective as a single dose
	hydrocephalus	clomiphene	1967	rat	*in vivo*	50	4.0	two cases — hydrocephalus and cranioshisis with gastroshisis, no control animals
Miller & Armstrong (1981)	decreased rate of implantation/ inhibition of implantation	PMSG	1981	rat	*in vivo*	84		no no-treatment control group, but there is a dose-related increase in implantation failure

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
White et al. (1981)	anovulation	clomiphene	1981	rat	*in vivo*			100.0	neonatal treatment of rats with cc-induced chronic persistent estrus (like androgen treatment)
Moon et al. (1989)	anovulation	clomiphene	1989	rat	*in vivo*		<0.0500	100.0	clomiphene acts to reduce ovulation in the hypophysectomized rat treated with estrogen
Basu (1972a)	uterine hyperplasia	clomiphene	1972	mouse	*in vivo*	20	< 0.0100		clomiphene has estrogenic properties when administered to the neonatal mouse (as measured by uterine hyperplasia)
Thomson (1968)	morulation rate decreased	clomiphene	1968	mouse	*in vitro*			100.0	cc is toxic to the two-cell embryo
Druga & Nyitray (1990)	cataracts	clomiphene	1990	rat	*in vivo*				clomiphene given to rats days 7-16 induced cataracts
Nicoletti et al. (1985)	epilepsy	clomiphene	1985	rat	*in vivo*	12			cc exhibits mild anti-convulsant effects at low doses but at high doses potential

									seizures
Souma et al. (1972)	reduced collagen content of bone	clomiphene	1972	rabbit	*in vivo*		< 0.0010	4.7	pregnant rabbits were treated with cc and the fetal weight was reduced due to reduction in collagen content of bone
Iguchi et al. (1989)	delayed/deficient endometrial maturation	clomiphene	1989	rat	*in vivo*				exposure to estrogen agonists or antagonists delayed normal luminal epithelial development pattern
Labhsetwar (1970)	anovulation	clomiphene	1970	rat	*in vivo*	66		100.0	cc blocks ovulation when given orally to cycling rats at estrus
Docke (1971)	anovulation	clomiphene	1971	rat	*in vivo*			87.5	cc blocks ovulation in adult and pre-pubertal rats
Amaury et al. (1972)	decreased rate of implantation/ inhibition of implantation	clomiphene	1972	rabbit	*in vitro*	89	< 0.0010	26.0	clomiphene inhibits blastocyst development in culture
Lopez-Escobar & Fridhandler (1969)	premature birth abnormality	clomiphene	1969		*in vitro*		n.s.	0.0	no increase in abnormality among oocytes treated with cc *in vitro* (oocyte metaphase aneuploidy)

Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Maudlin & Fraser (1977)	chromosomal abnormality	PMSG	1977	mouse	*in vivo*				there is a dose-dependent increase in chromosomal abnormalities among mouse embryos fertilized *in vitro*
Zambrano et al. (1982)	blastogenesis	clomiphene	1982	mouse	*in vitro*	12	n.s.	0.0	no increase in blastogenesis among 10 mice treated with cc orally for four days and assessed with the micronuclei assay
Cunha et al. (1987)	abnormal genital tract	clomiphene	1987	human	*in vivo*	54			human reproductive tissues inserted into the renal capsule of the athymic mouse and given cc developed changes similar to DES in terms of estrogenicity; however, no adenosis was observed; there was marked inhibition of endometrial gland development; changes in mesenchymal morphogenesis were present

(1989)	epithelium								lesions found in 33 day-old mice given neonatal cc
Clark & McCormack (1977)	abnormal genital epithelium	clomiphene	1977	rat	*in vivo*			80.0	neonatal treatment of rats produced atrophic ovaries, atrophic uterus, hypertrophy of oviduct, uterine metaplasia
Spadoro et al. (1982)	malformations	clomiphene	1982	rat	*in vitro*				cc is responsible for an increase in anomalies in rats cultured *in vitro*
Clark & McCormack (1980)	abnormal genital tract epithelium	clomiphene	1980	rat	*in vivo*				rats trialed in pregnancy have offspring with multiple abnormalities of the genital tract (disorganized epithelium, atypical epithelium, metaplastic epithelium, degenerating epithelium or cyst in vagina, cervix, uterus, and oviduct)
Yoshimura et al. (1986)	morulation	clomiphene	1986	rabbit	*in vitro*	18	< 0.0050	33.5	cc reduces rate of morulation and increases

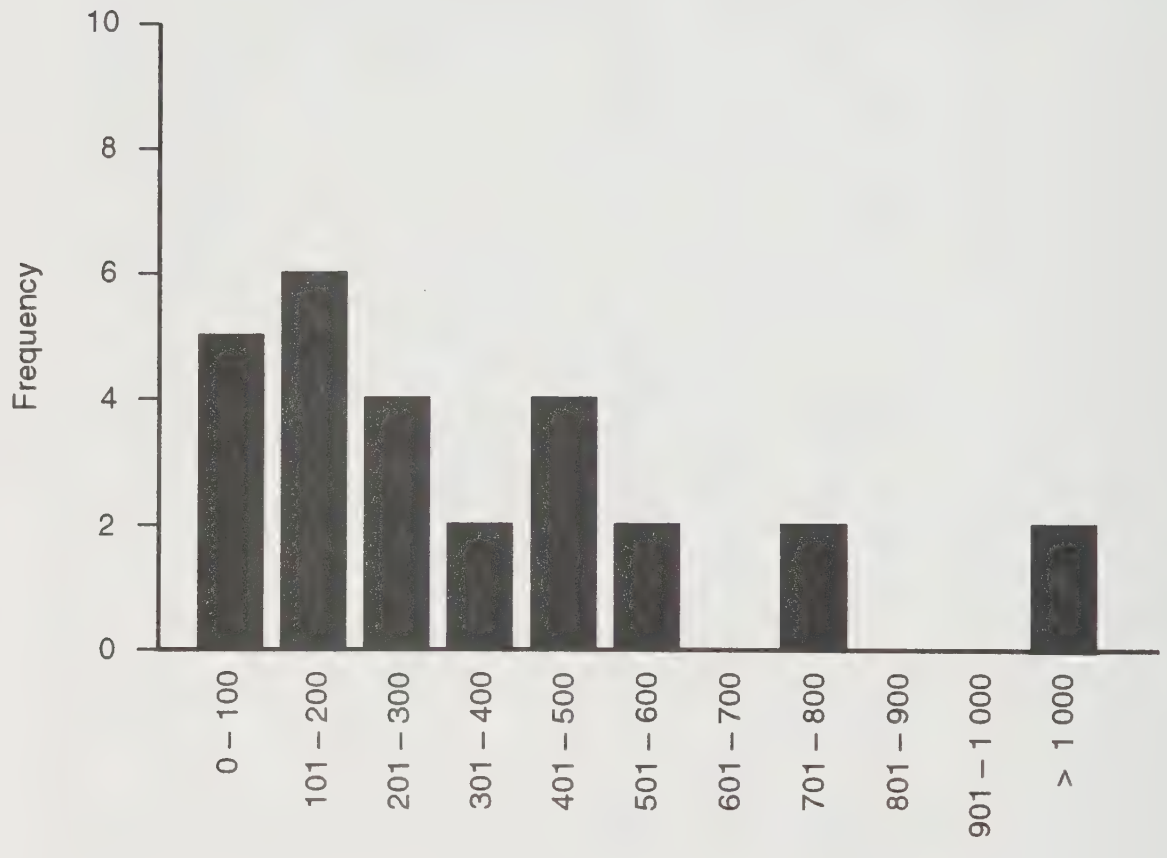
Table 11. (*cont'd*)

Author(s)	Outcome	Drug	Date	Species	Design	Total	Probability	Effect size (%)	Comments
Yoshimura et al. (1986)	degeneration	clomiphene	1986	rabbit	*in vitro*	18	< 0.0500	27.6	degeneration of eggs from *in vitro* perfused rabbit ovaries
McCormack & Clark (1979)	abnormal reproductive tract	clomiphene	1979	rat	*in vivo*	40			a single injection of cc during pregnancy caused multiple abnormalities of genital tract in offspring (cervix, uterus, and tube)
Thomson (1968)	reduced implantation	clomiphene	1968	mouse	*in vivo*	120		100.0	delay in transport of embryos to uterus and reduction in implantation
Yoshimura et al. (1987)	morulation, blastulation	clomiphene	1987	rabbit	*in vitro*	42		19.1	estrogen improves morulation rate of ova derived from rabbit ovaries induced to ovulate after cc treatment
Birkenfeld et al. (1985a)	reduced implantation	clomiphene	1985	rabbit	*in vivo*			44.0	recipient before ovulation (uterus)
							42.0000	42.0	recipient after ovulation (uterus)

									(egg)
								0.0	donor after ovulation
									cc has an effect on endometrium, tubal physiology, and ovum maturation before ovulation interfering with blastocyst function
Schmidt et al. (1986)	embryo development	clomiphene	1986	mouse	*in vitro*	381 embryos	< 0.0010	96.0	cc causes degeneration of mouse embryo 4 to 8-cell stage

n.s. — not significant.

Figure 1. Frequency of Total of New Patients Seen in Clinic per Year



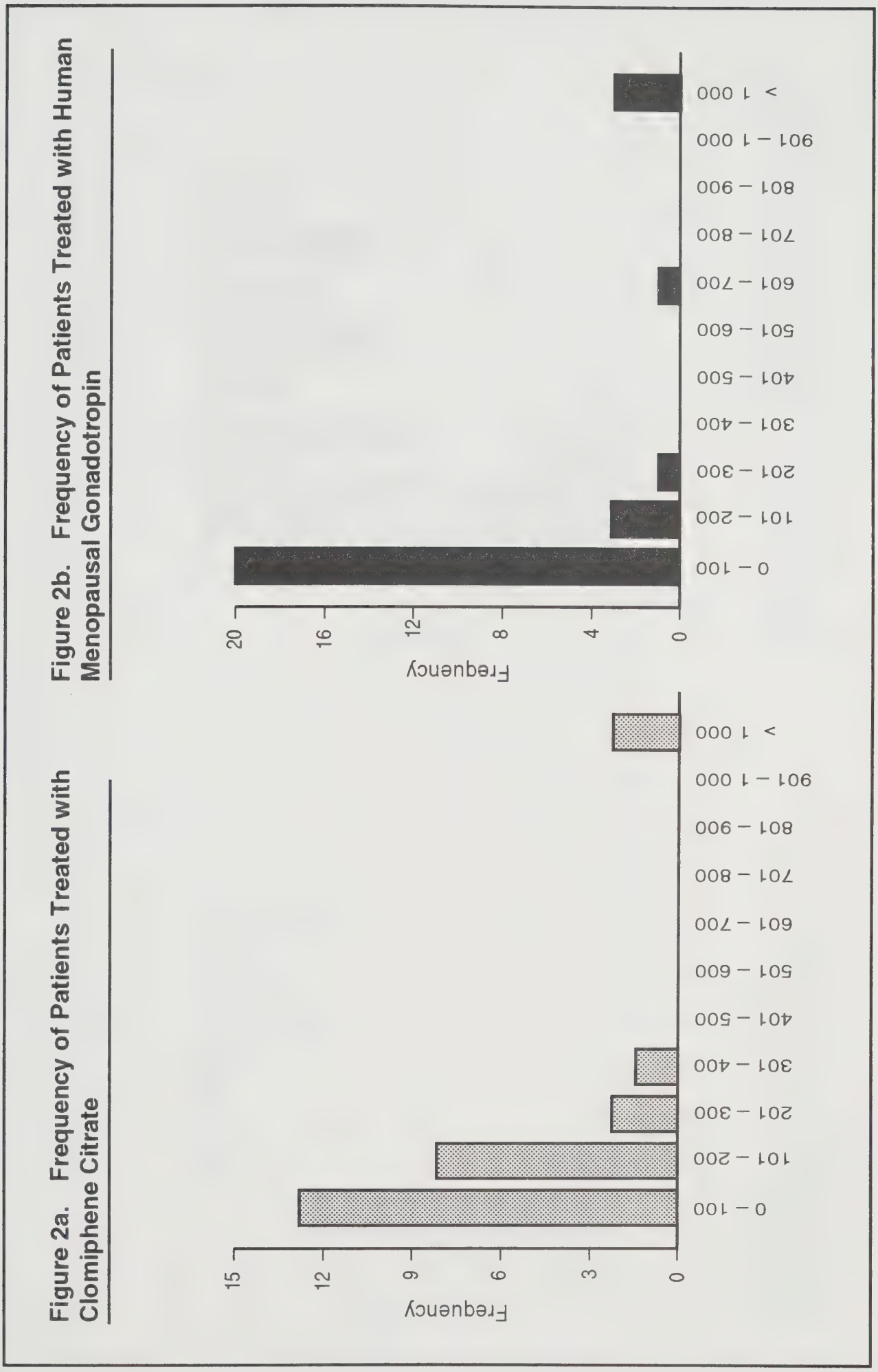


Figure 2a. Frequency of Patients Treated with Clomiphene Citrate

Figure 2b. Frequency of Patients Treated with Human Menopausal Gonadotropin

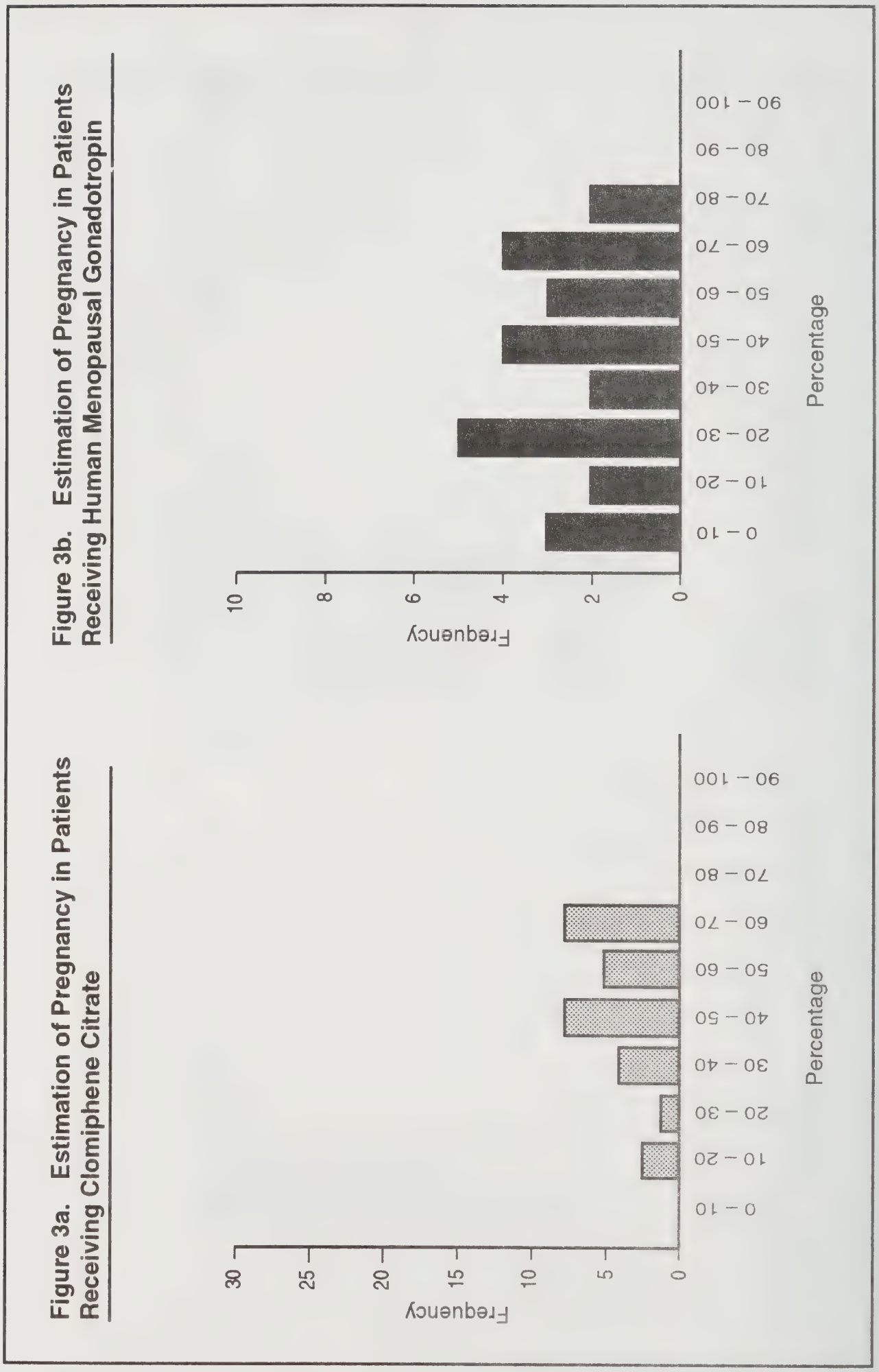
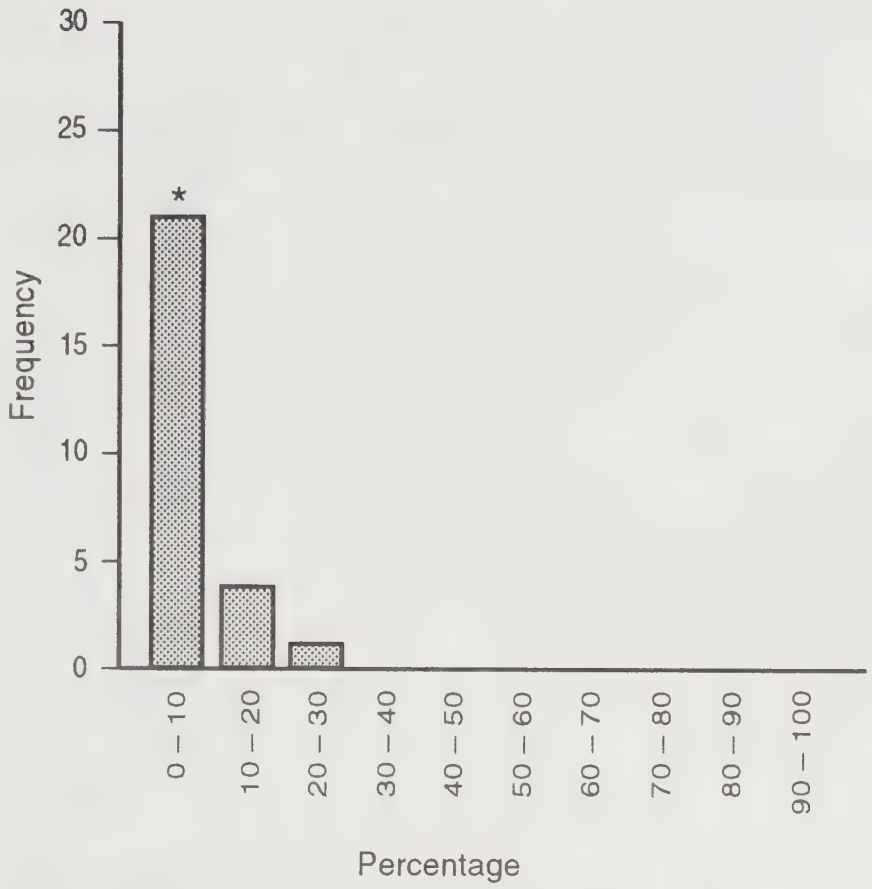
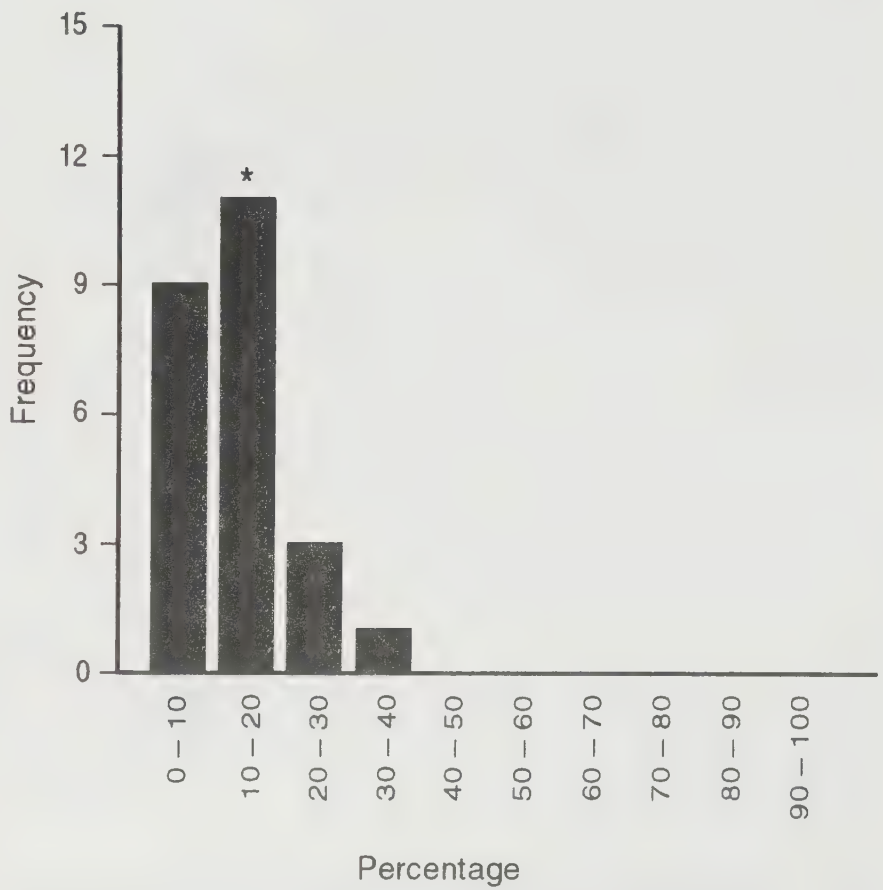

Figure 3a. Estimation of Pregnancy in Patients Receiving Clomiphene Citrate
Frequency
30
25
20
15
10
5
0
0 – 10
10 – 20
20 – 30
30 – 40
40 – 50
50 – 60
60 – 70
70 – 80
80 – 90
90 – 100
Percentage
Figure 3b. Estimation of Pregnancy in Patients Receiving Human Menopausal Gonadotropin
Frequency
10
8
6
4
2
0
0 – 10
10 – 20
20 – 30
30 – 40
40 – 50
50 – 60
60 – 70
70 – 80
80 – 90
90 – 100
Percentage

Figure 4a. Estimation of Twins in Patients Receiving Clomiphene Citrate



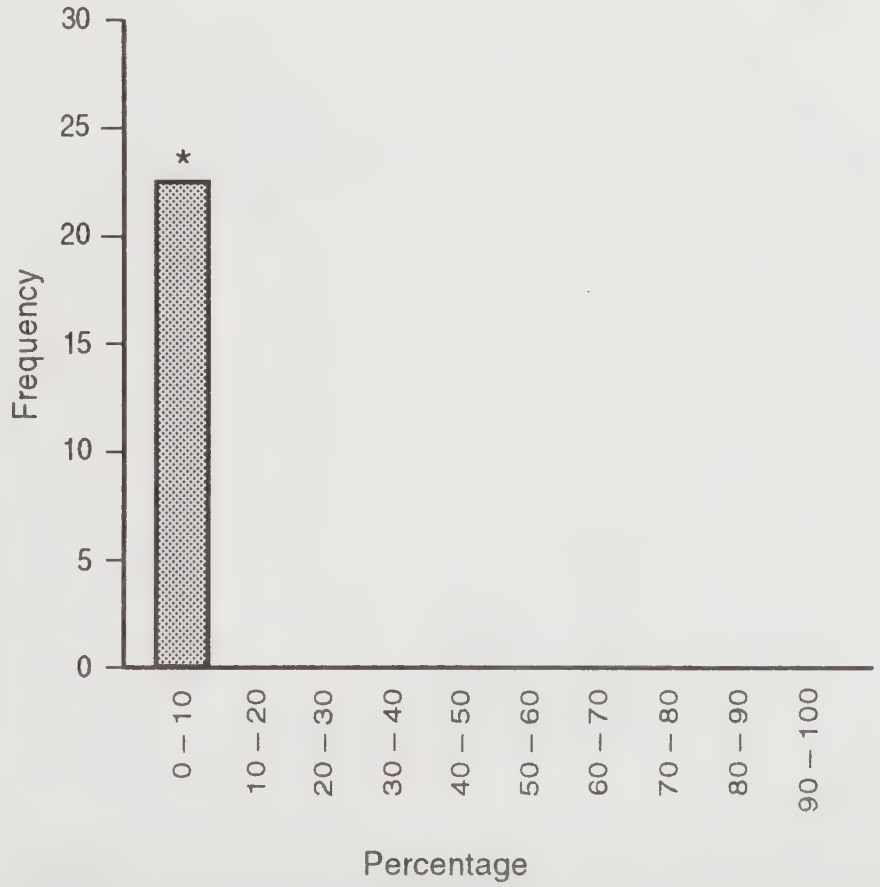
* Meta-analysis calculated rate

Figure 4b. Estimation of Twins in Patients Receiving Human Menopausal Gonadotropin



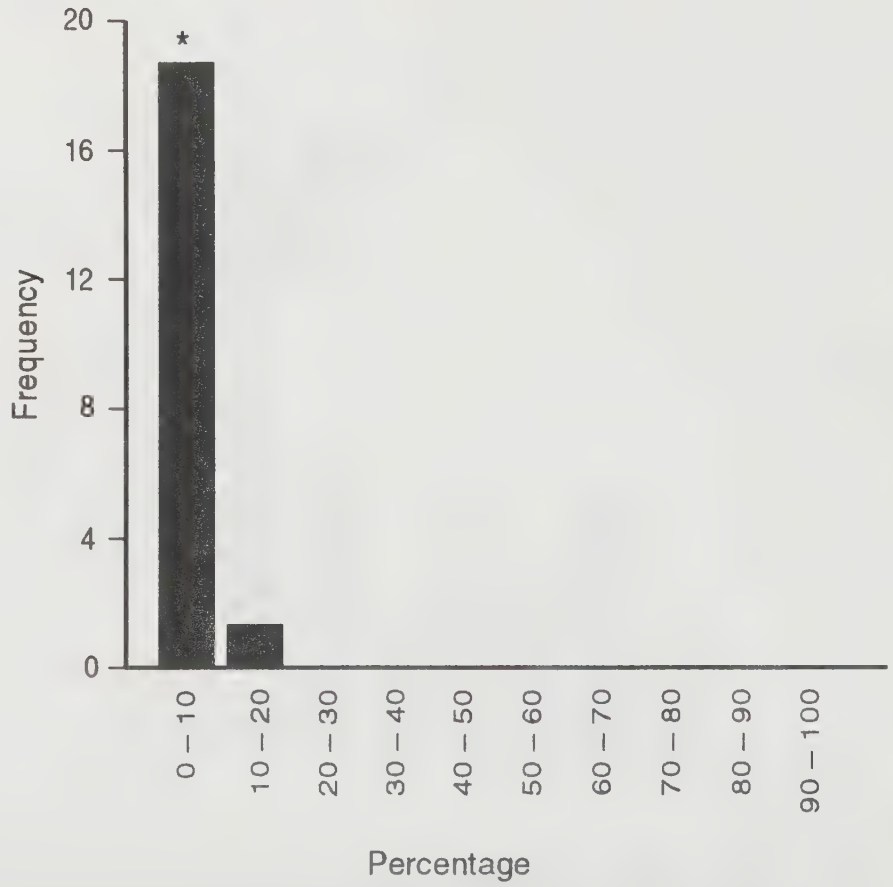
* Meta-analysis calculated rate

Figure 5a. Estimation of Triplets in Patients Receiving Clomiphene Citrate



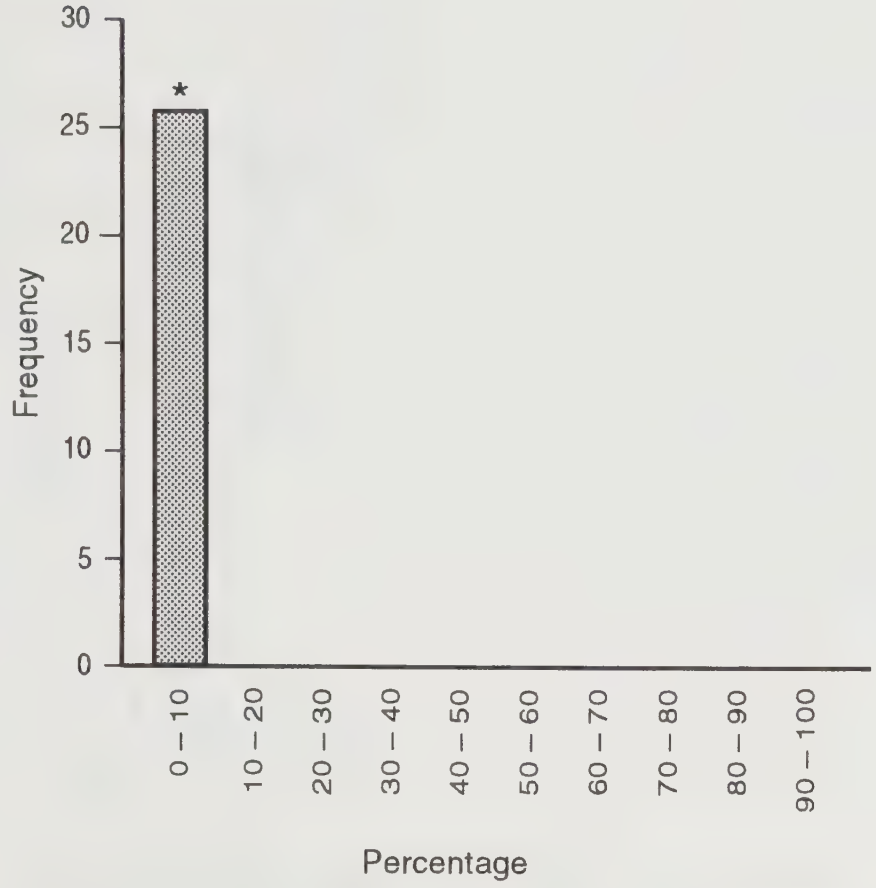
* Meta-analysis calculated rate

Figure 5b. Estimation of Triplets in Patients Receiving Human Menopausal Gonadotropin



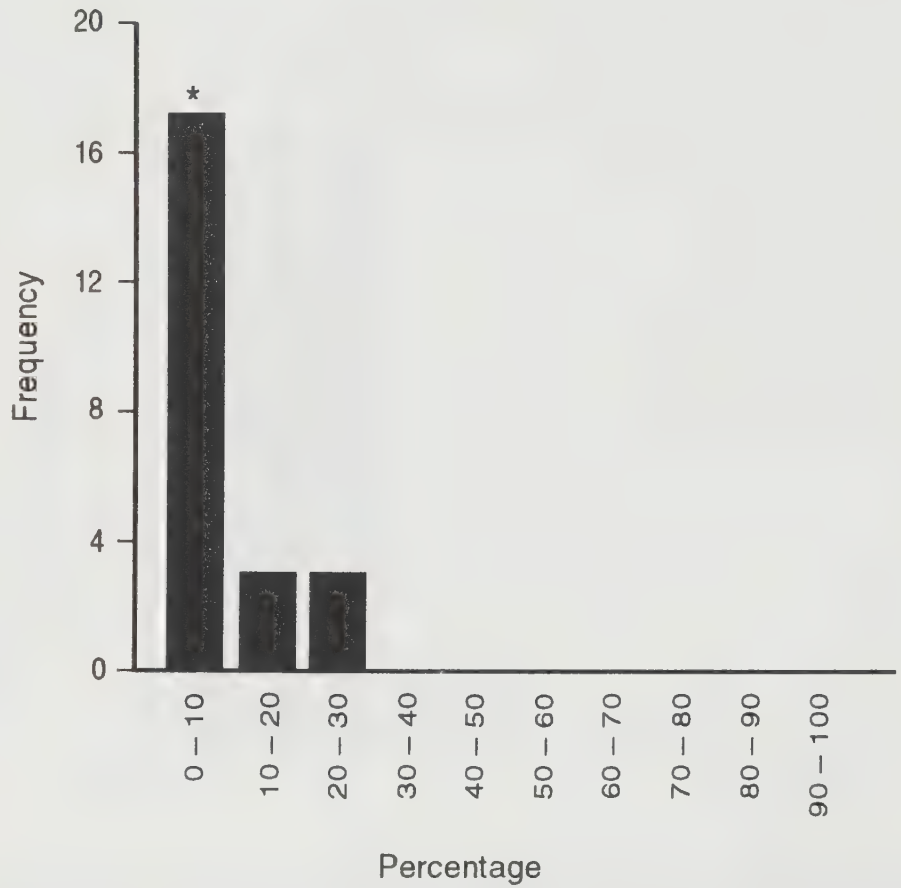
* Meta-analysis calculated rate

Figure 6a. Estimation of Hyperstimulation in Patients Receiving Clomiphene Citrate



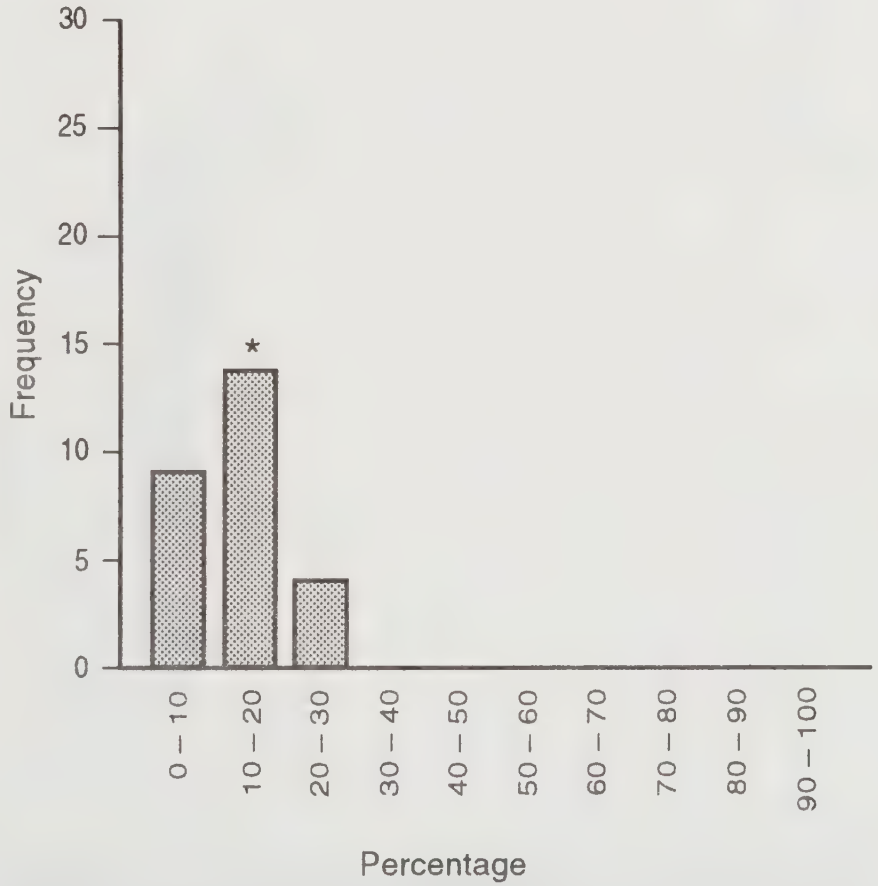
* Meta-analysis calculated rate

Figure 6b. Estimation of Hyperstimulation in Patients Receiving Human Menopausal Gonadotropin



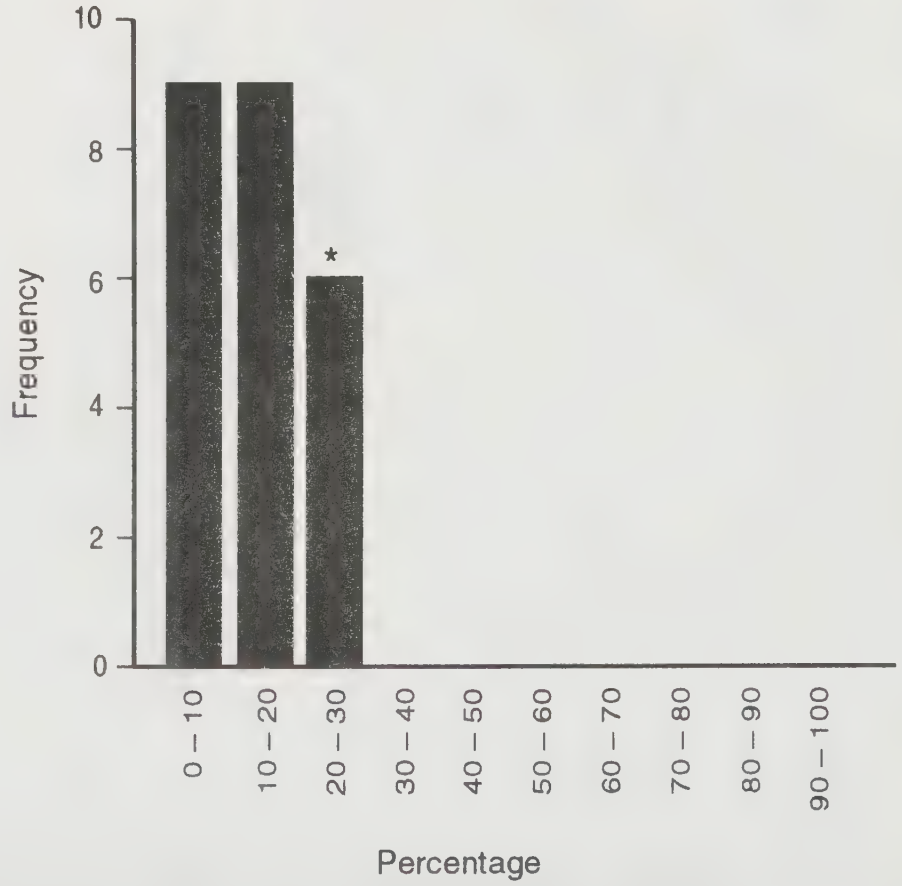
* Meta-analysis calculated rate

Figure 7a. Estimation of Spontaneous Abortions in Patients Receiving Clomiphene Citrate



* Meta-analysis calculated rate

Figure 7b. Estimation of Spontaneous Abortions in Patients Receiving Human Menopausal Gonadotropin



* Meta-analysis calculated rate

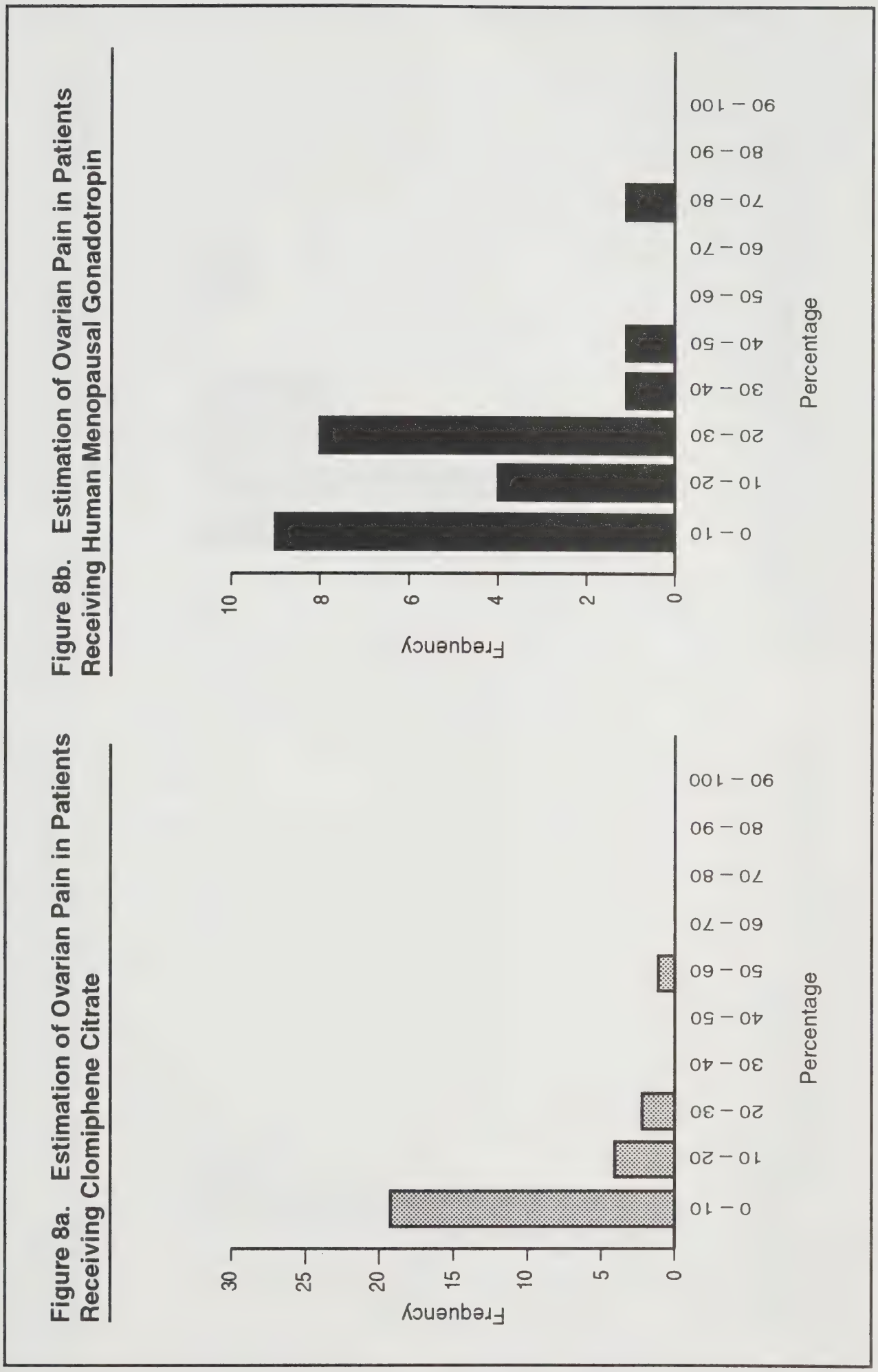


Figure 8a. Estimation of Ovarian Pain in Patients Receiving Clomiphene Citrate

Figure 8b. Estimation of Ovarian Pain in Patients Receiving Human Menopausal Gonadotropin

Figure 9a. Estimation of Ovarian Cysts in Patients Receiving Clomiphene Citrate

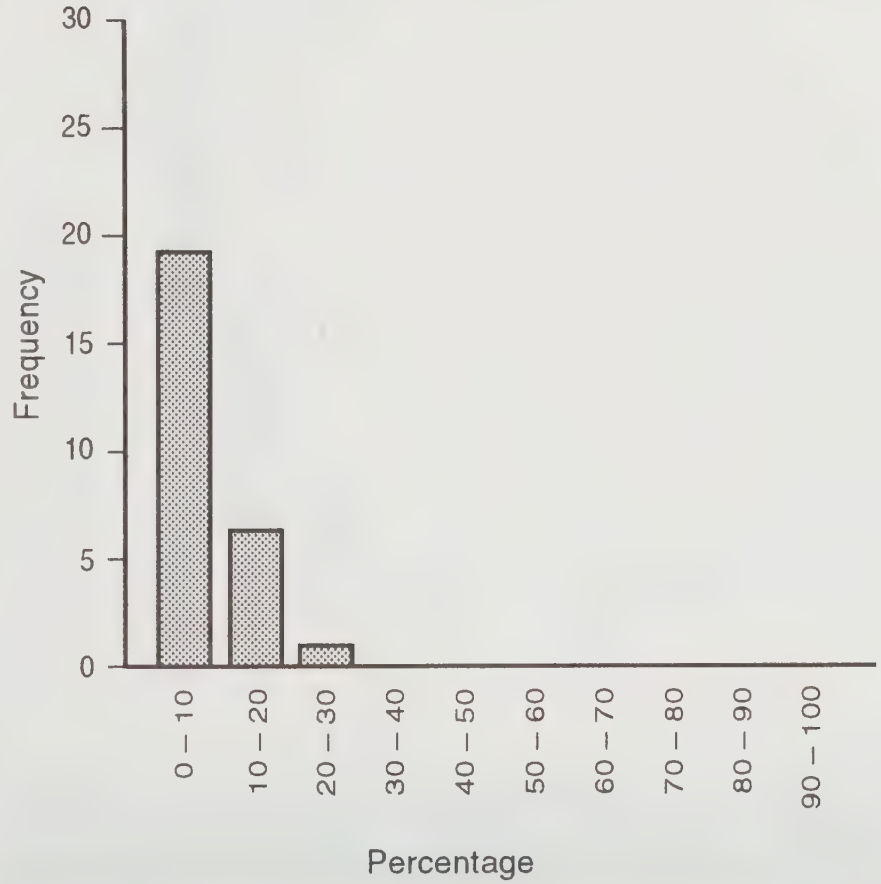
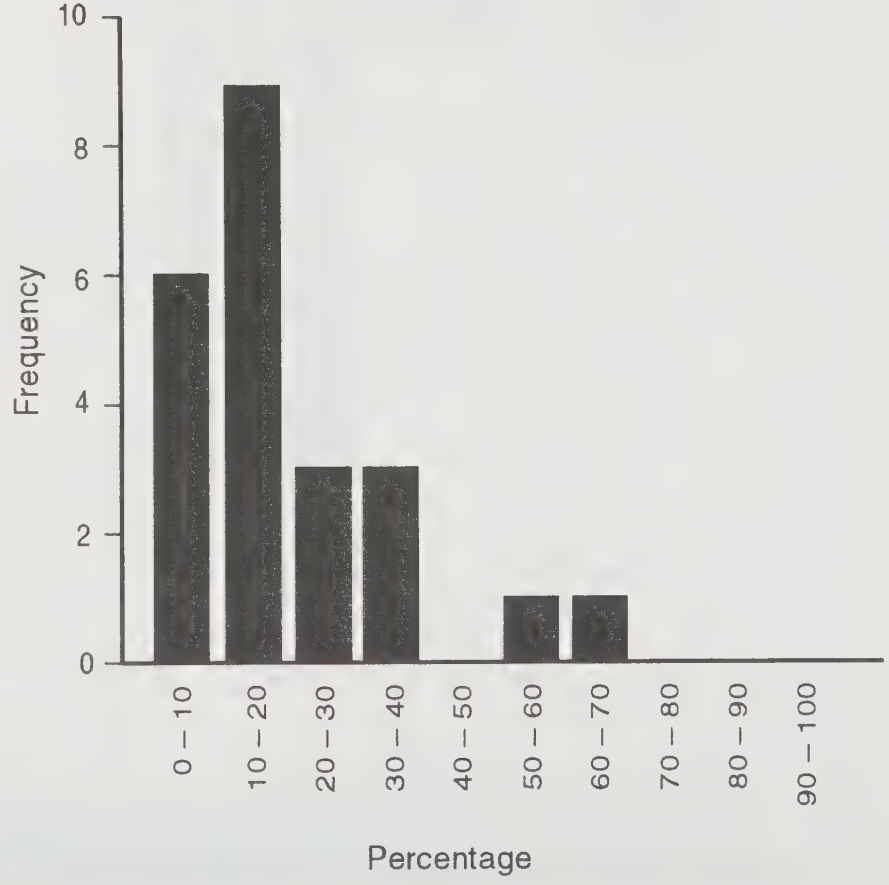


Figure 9b. Estimation of Ovarian Cysts in Patients Receiving Human Menopausal Gonadotropin



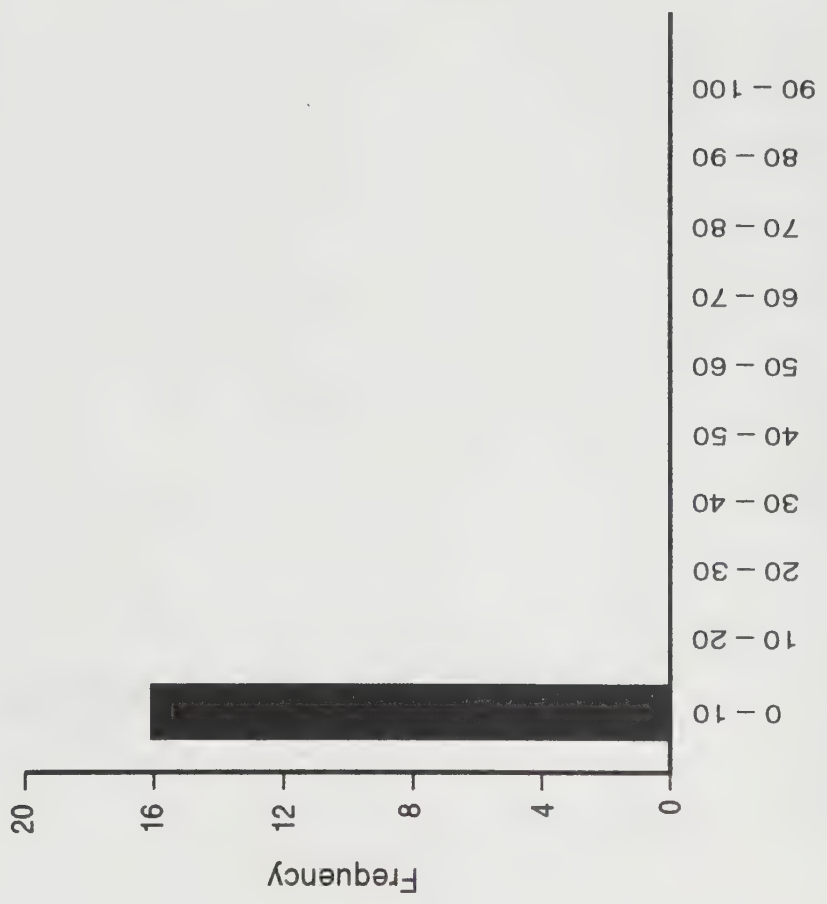


Figure 10b. Estimation of Other Malformations in Patients Receiving Human Menopausal Gonadotropin

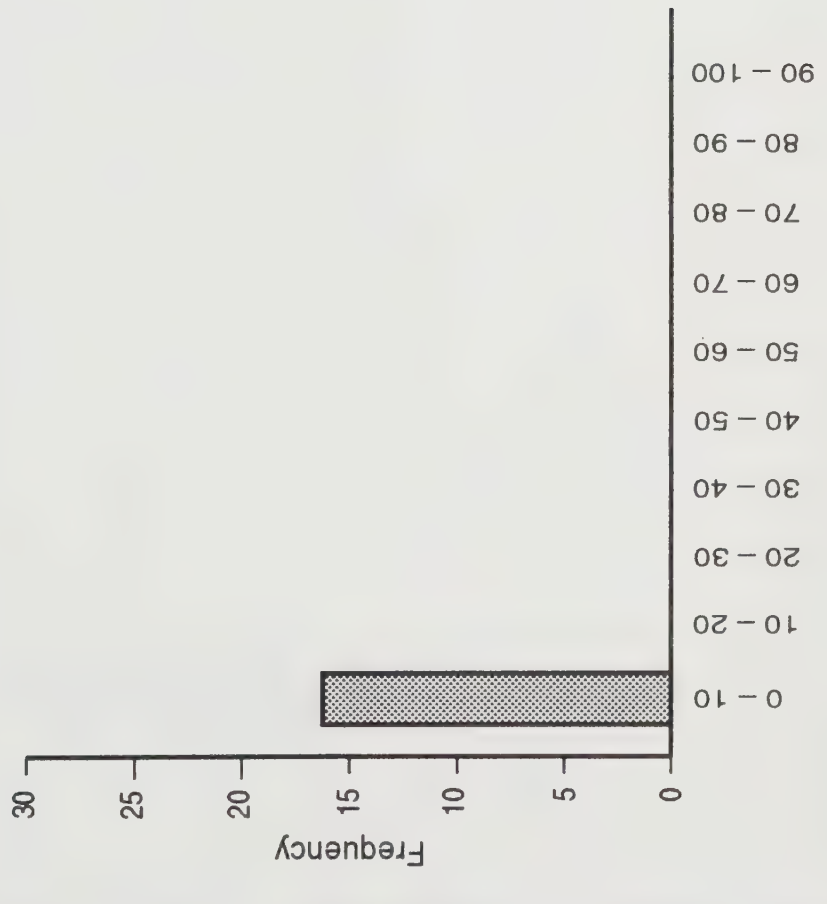


Figure 10a. Estimation of Other Malformations in Patients Receiving Clomiphene Citrate

Figure 11a. Estimation of Anencephaly in Patients Receiving Clomiphene Citrate

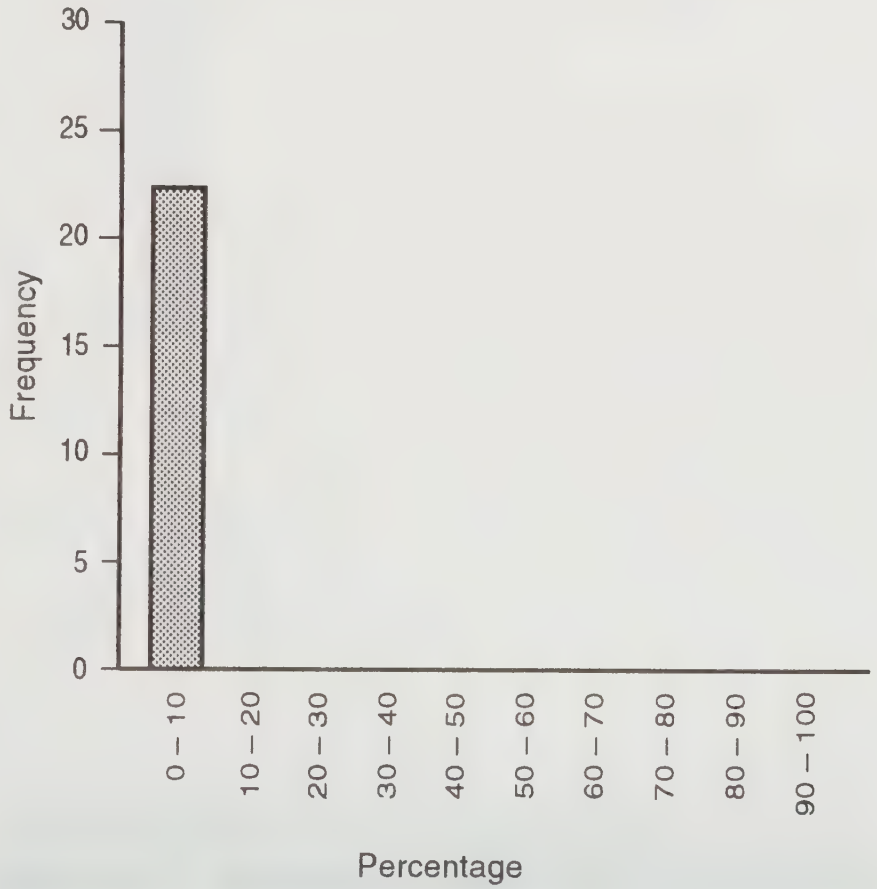
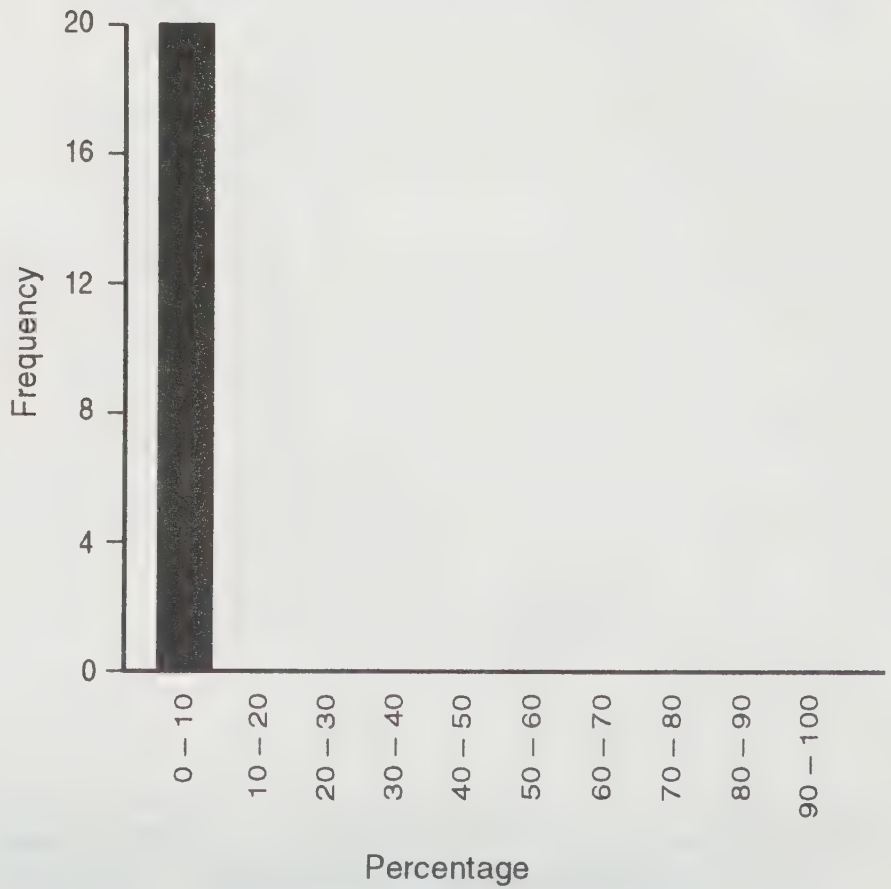


Figure 11b. Estimation of Anencephaly in Patients Receiving Human Menopausal Gonadotropin



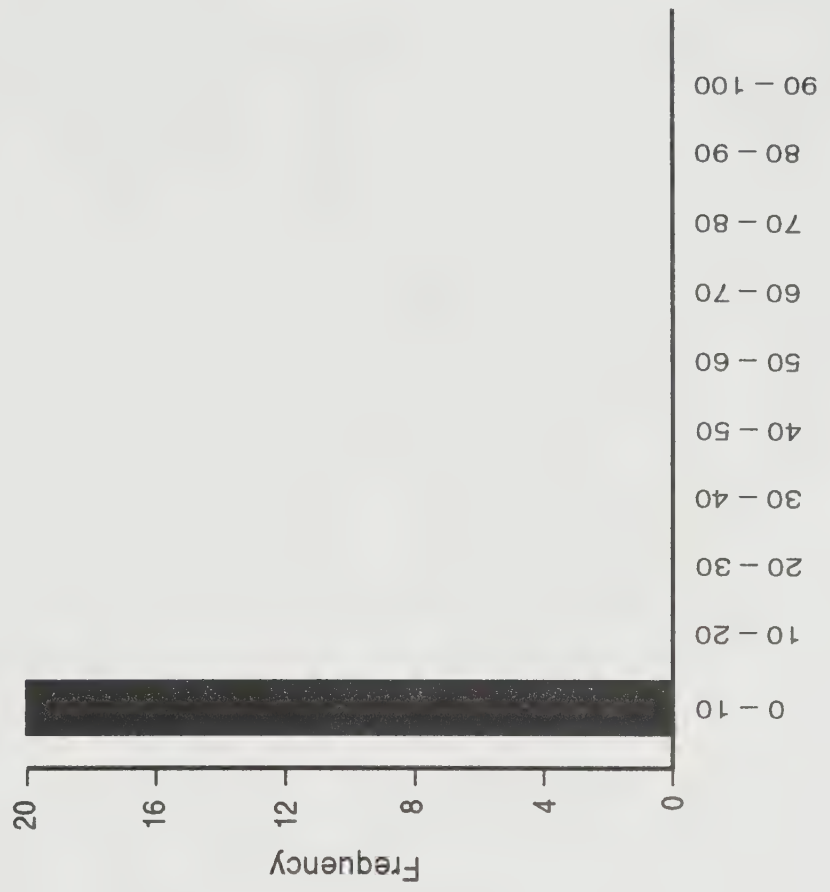


Figure 12b. Estimation of Spina Bifida in Patients Receiving Human Menopausal Gonadotropin

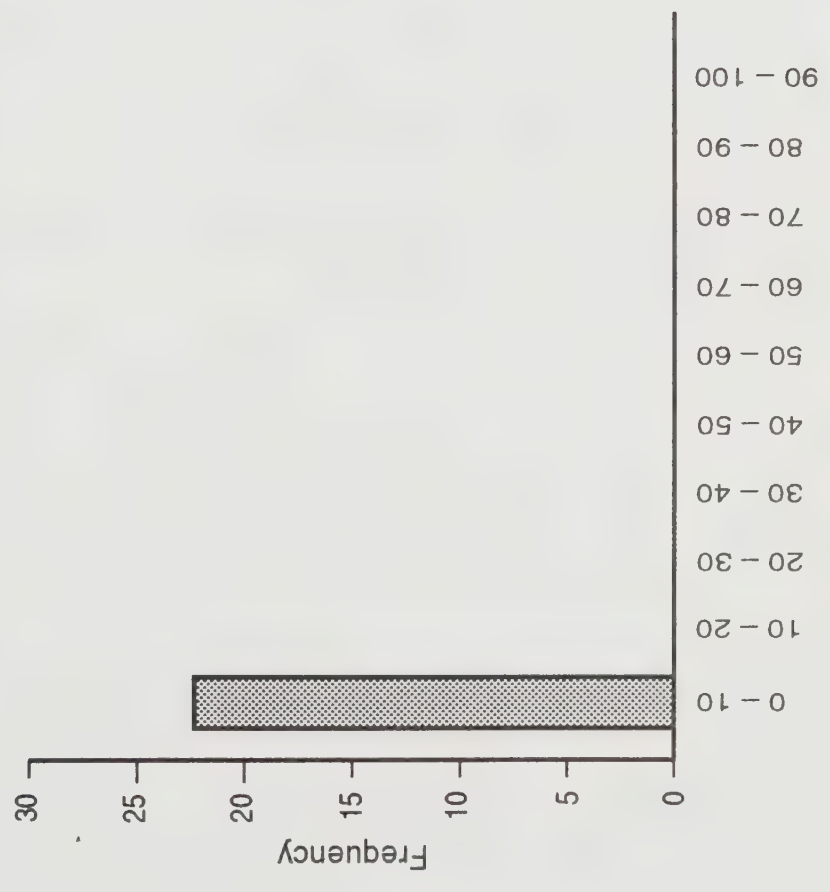


Figure 12a. Estimation of Spina Bifida in Patients Receiving Clomiphene Citrate

Discussion

This report contains a large amount of information regarding the adverse health effects related to the most commonly used methods of ovulation induction. Although every attempt has been made to be comprehensive, several studies that could and should be added have not been included because of the many factors that have been mentioned throughout this document. However, a continuation of this process is being considered and may provide a vehicle for updating the data base.

Perhaps the most relevant comment that can be made is that this is the first comprehensive attempt to compile relevant adverse effects. Many studies have been carried out with individual subjects, yet the overall picture indicates that the agents are immensely powerful drugs and that there has been a relative vacuum in terms of the attention directed toward the outcomes. In comparison, drugs used for chemotherapy and cardiac arrhythmias are extensively reviewed for their side-effects. It can be argued that the potential for adverse health effects in young women having families is as great as or greater than that associated with the treatment of cancer or heart disease.

In compiling this data base, one of the most obvious reasons for the lack of effect sizes that can be combined is the relative paucity of randomized controlled clinical trials. There was only one randomized controlled trial of IVF compared to "no treatment" which permitted a comparison of the rates of adverse pregnancy outomces (Jarrel et al. 1993). Because most documented adverse outcomes were reported as secondary outcomes within the studies, conducting meta-analysis was usually impossible and combining crude rates was difficult and limited.

The processes involved in the combined crude rate analysis have, to our knowledge, never been attempted. Combining reported crude rates helps to determine the rate at which adverse outcomes occur, but it lends itself to many limiting factors as well.

As with many measures of the rate of occurrence or incidence of disease in a given population, the stability of a reported rate is highly dependent on the number of subjects studied. In looking at rates associated with exposure to clomiphene, there are a number of outcomes for which the number of subjects studied exceeded 1 000. The rates for these outcomes, with such high denominators, are expected to be stable and to provide good estimates, based on what is reported in the medical literature, of the "true" rates. For example, the estimated rates of nausea/vomiting (2.2%), ovarian enlargement (13.6%), breast pain (2.0%), and multiple birth (7.85%) with clomiphene exposure are all expected to be close to the true rates since they were derived by observing many subjects.

Another factor that impacts on the confidence of the reported combined crude incidence rates pertains to the number of articles upon which a particular rate is based. Looking at Table 10, for example, the rate

of abdominal pain (92%) associated with exposure to hMG was based on only one study, and even though the number of subjects was large (2 553), it cannot be said that the rate observed is highly reflective of the true rate. The reason for the lack of confidence when the number of studies is small is that constraints within the individual study restrict generalizing the combined result. For combined rates based on many studies, generalizing the result improves as the variability of the sample population increases.

Combined crude rates are especially subject to the phenomenon referred to as publication bias. Many of the studies used to compute the combined rates were not explicitly designed to test the association between exposure to ovulation-inducing drugs and any particular adverse outcome. These studies reported that a certain number of cases of an adverse effect occurred in a population of women undergoing treatment; if no cases of the adverse outcome were seen, this was likely not reported.

The extent of the effect of publication bias is highly dependent on the study design and the particular adverse outcome. Publication bias is less, but still exists, for studies carried out to assess the impact of a treatment on the outcome of interest. In Table 8, the study designs are not specified, largely due to the problem that segregating rates by outcome and then by design resulted in small numbers within each stratum. The nature of the adverse outcome affects the potential for publication bias, as few studies that reported uncommon adverse outcomes were located.

How the adverse outcomes are measured affects both the reliability and validity of the combined reported crude rates. Outcomes such as malformation (major), sex ratio, and multiple births have measures that are reliable and valid both within and between studies. Adverse outcomes are not uncommon with respect to studies on the effects of infertility drugs; therefore, they are reported regularly, which also reduces the likelihood of publication bias.

The meta-analyses on sex ratio and congenital malformations are extensions to the combination of crude rates and are subject to the same limitations. These outcomes are determined and reported on a routine basis, and their measures are highly reliable. The probability of obtaining the number of male children born was based on the widely accepted probability of the birth of a boy being 106:100. The probability of obtaining the observed number of malformations for each study and for all studies combined was often based on the average probability of a particular malformation, which was computed on the basis of the rates reported for unexposed populations.

Given the way in which the probabilities of the expected number of malformations were computed, the reported values should be interpreted with caution. Table 4, which presents the combined rates of NTDs and congenital malformations, also provides 95% CIs for the combined estimates of rates. In all cases, the average reported (unexposed) rates were within the CIs reported in the exposed groups.

All of the meta-analysis procedures used, including the meta-analysis of case-control studies of NTDs, were based on the assumption that the true effect of exposure was the same in each of the individual studies that were combined. The assessment of the interaction of study and exposure by logistic regression in the analysis of case-control studies provided a formal test of this assumption. In this situation, there was no evidence of statistical heterogeneity, but one cannot rule out the effect of the inevitable differences due to differences in the assessment of exposure, definitions of cases, characteristics of patient and control subject populations, and numerous other factors that would be expected to vary across these studies. Therefore, the combined odds ratio, even though there was no evidence of statistical heterogeneity, should be interpreted with caution.

Several important conclusions can be drawn from the literature review. First, from the animal studies, many aspects of measurable reproduction can be altered by the administration of clomiphene citrate. It is difficult to determine the effects of hMG on animals because of the lack of adverse reproductive studies reported in the literature. The relationship between the clomiphene animal study results and human health is not known.

Regarding human response to ovulation induction with clomiphene, the adverse outcomes are measurable in terms of gastrointestinal and nervous system symptoms and in more outcomes that relate to the urogenital system and various aspects of pregnancy. The use of hMG in association with other drugs appears to enhance these frequencies, particularly for spontaneous abortion, heterotopic pregnancy, and multiple births of various degrees. An increase in fetal reduction may be expected; thus, this procedure should be pursued carefully for both effectiveness and safety. In addition, information related to the outcomes of IVF, such as abnormal chromosomal configuration of oocytes and embryos in association with altered cleavage rates, is reminiscent of the animal studies, emphasizing the danger of ignoring animal experimentation.

The results obtained from the Canadian infertility clinic survey suggest that most clinics are aware of the most prevalent adverse outcomes related to ovulation induction. However, the combined occurrences of the adverse health effects of ovulation induction, as perceived by the patient, may be overlooked or classified as physiologic responses rather than as overt adverse outcomes.

With regard to ovarian cancer, the addition of a few case reports to the existing body of literature does not constitute sufficient evidence for a link between ovulation induction and ovarian cancer, nor does it remove it from suspicion. Past epidemiologic studies have not singled out fertility drugs when examining an association between infertility and ovarian cancer. However, current epidemiologic studies are including infertility drugs as a factor of concern. The results from these studies may provide more conclusive evidence for a link between ovulation induction and ovarian cancer.

Long-term follow-up in the treatment of infertility has only recently been identified as a valuable or desirable objective, and these registries are

still predominantly directed to successful clinical pregnancy. It is fair to say that there has not been sufficient concerted attention directed to the frequency, mechanisms, or impact of the adverse outcomes of drug use in ovulation induction.

Hypothetically, the process of informed consent in the clinical encounter could be compromised. There is a relative imbalance between the possibility of a successful pregnancy and relevant adverse health outcomes. A more comprehensive evaluation of outcomes will result in a more informed patient, one capable of making appropriate decisions related to fertility treatment.

The following recommendations are made in the interest of the health and safety of women seeking fertility treatment:

1. provide appropriate informed consent. Before administering drugs for ovulation induction, the following concepts should be addressed with the patient:
   (a) clomiphene citrate has been shown to be toxic to the reproductive system in many animal species, and the significance of many of these observations is unknown;
   (b) treatment with clomiphene citrate is associated with the following adverse health effects:

(i)	abortion rate	20.0%
(ii)	ectopic pregnancy rate	1.6%
(iii)	multiple pregnancy rate	8.0%
(iv)	heterotopic pregnancy rate	0.5%

   (v) no increase in congenital malformations, a slight increase in NTDs, and a change in the sex ratio (94 males per 100 females);
   (c) treatment with hMG is associated with the following adverse health effects:

(i)	abortion rate	25.0%
(ii)	multiple pregnancy rate	20.0%
(iii)	twins	13.0%
(iv)	triplets	2.0%
(v)	quadruplets	< 1.0%
(vi)	quintuplets	< 1.0%
(vii)	heterotopic pregnancy rate	3.0%
(viii)	ectopic pregnancy rate	3.0%

   (ix) no increase in congenital malformations, a slight increase in NTDs, and no change in the sex ratio;

2. monitor selected reproductive outcomes identified as toxic in animal species. Specifically, based upon the animal studies presented, humans exposed to clomiphene *in utero*, either for ovulation induction or due to an error in medication, should be assessed for vaginal adenosis;
3. educate relevant health professionals regarding the existence of and difficulty in diagnosing heterotopic pregnancy. General practitioners and emergency room physicians should be informed of heterotopic pregnancy among these selected patients; and
4. support a comprehensive assessment of adverse reproductive health effects from ovulation induction.

Appendix 1

Drugs Used in Infertility Therapy

Female:

1. Ovulation induction
   - Clomiphene
   - hMG (Pergonal®)
   - hCG
   - Bromocriptine (Parlodel®)
   - Estrogen
   - Radiation
   - Pure FSH
   - Glucocorticoids
   - Tamoxifen
2. Ovulation suppression
   - Danazol®
   - GnRH agonists
   - GnRH antagonists
   - Progesterone (Medroxy Progesterone — MPA)
   - Testosterone
3. Luteal phase
   - Progesterone
   - Use of immunization
   - ASA
   - DES
   - Prednisone

Male:

1. Testosterone
2. Clomiphene
3. hMG
4. hCG
5. Bromocriptine
6. GnRH agonists
7. Tamoxifen (increase sperm motility)
8. Methylxanthines (e.g., caffeine, pentoxifylline)
9. Kallikrein
10. Vitamin B_{12}
11. Phenelzine sulphate (Nardil)
12. Calcium antagonist
13. Arginine
14. Fluoxymesterone
15. Glucocorticoids

Clomiphene (two forms)

(1) Chemical name: triethylamine, 2-(p-(2-diphenylvinyl) phenoxy)

Chemical Abstracts Service Registry Number: 911-45-5 (clomiphene)

Synonyms/trade names:
:chlomaphene
:chloramifene
:chloramiphene
:cisclomiphene
:clomifene
:clomiphene
:clomiphene B
:clostilbegyt (Hung)
:2-(4-(2-chloro-1,2-diphenylethenyl)phenoxy)-n,n-diethylethanamine
:2-(p-beta-chloro-alpha-phenylstyryl)phenoxy)-triethylamine
:1-(p(beta-diethylaminoethoxy)-phenyl)-1,2-diephenylchloroethylene

(2) Chemical name: triethylamine, 2-(p-(2-chloro-1,2-diphenylvinyl) phenoxy)-, citrate (1:1)

Chemical Abstracts Service Registry Number: 50-41-9 (citrate)

Synonyms/trade names
:chloramiphene
:chloramiphene citrate
:Clomid® (Merrell Dow Pharmaceuticals)
:clomifen citrate
:clomifeno

:clomiphene citrate
:clomiphene dihydrogen citrate
:clomiphene-r
:clomiphine
:clomivid (Den, Swd, Nor)
:clomphid
:dyneric (Germ)
:genozym (Arg)
:ikaclomin
:mer-41
:mrl 41
:nsc 35770
:omifin (Spain)
:pergotime (Den, Fr, Germ)
:prolifen (Chiesi, Ital)
:racemic clomiphene citrate
:Serophene® (Pharmascience Inc.)
:2-chloro-1-(p-(beta-diethylaminoethoxy)phenyl)-1,2-diphenyl-ethylene
:2-(p-(2-chloro-1,2-diphenylvinyl)phenoxy) triethylamine dihydrogen citrate
:2-(p-(2-chloro-1,2-diphenylvinyl)phenoxy) triethylamine citrate (1:1)
:1-(p-(beta-diethylaminoethoxy)phenyl)-1,2-diphenyl-2-chloro-ethylene citrate

(3) Other Chemical Abstracts Service Registry Numbers:
- 15690-57-0 (clomiphene, E)
- 15690-55-8 (clomiphene, Z)
- 7599-79-3 (citrate, E)
- 7519-53-6 (citrate, Z)
- isomers: zuclomiphene and enclomiphene

Usage:
- ovulation induction
- amenorrheic with hyperestrogenic
- hyperandrogenic
- acyclic form of amenorrhea (POD)
- pituitary tumours

History:
- 1956 synthesized
- 1959 patent to Merrell Dow
- 1960 clinical trials
- 1967 FDA approval

Adverse effects:
- multiple pregnancy (gestation)

- birth defects (anomalies)
- stillbirth, abortion
- sex ratio
- ovarian enlargement (ovarian hyperstimulation syndrome)
- ovarian cysts
- cervical mucus (quality and quantity)
- effects on liver function (bromsulphthalein) retention
- cataract formation
- teratogenicity in animal studies
- common symptomatic adverse effects:
  - hot flashes, abdominal discomfort, visual symptoms (blurring, scotomas, flashes), nausea or vomiting, dizziness, light-headedness, increased nervous tension, depression, fatigue, headache, insomnia, urticaria, allergic dermatitis, breast soreness, heavier menses, increased urinary frequency and volume, reversible hair loss, weight gain
- suspect effects:
  - mammary cancer, toxaemia, fetal ovarian dysplasia, maternal psychosis, congenital retinopathy

Human chorionic gonadotropin (hCG)

Chemical Abstracts Service Registry Number: 9002-61-3

Synonyms/trade names:

:antelobine
:antophysin
:Antuitrin S
:A.P.L.®
:apoidina
:BayHCG
:CG
:choragon
:choriogon
:choriogonadotrophin
:choriogonin
:choriomon
:chorion
:coriantin
:endocorion
:entromone
:ferti-cept
:follutein
:gestasol dry
:glanduantin
:glukor

:gonadex
:gonadotrafon LH
:gonadotraphon LH
:gonan
:gravimun
:harvatropin
:kortrin
:libigen
:lutormone
:neo-gonadil
:physex
:physostab
:predalon
:pregnesin
:pregnyl
:primogonyl
:Profasi®
:prolan
:PU
:randonos

Usage:

- ovulation induction
- cryptorchidism in males
- delayed adolescence
- dwarfism (pituitary)
- hypogonadotropic eunuchoidism
- hypogonadism after sexual maturity
- habitual abortion
- infrequent scanty bleeding (functional)
- treatment of obesity (no evidence to support its value)

Adverse effects (known or suspect):

- headache
- irritability
- restlessness
- depression
- tiredness
- edema
- precocious puberty
- gynaecomastia
- aggressive behaviour
- pain at injection site
- mutagenic effects in animals; humans
- fetal toxicity when administered during pregnancy
- enlargement of pre-existing ovarian cysts and possible rupture
- ovarian hyperstimulation syndrome

- growth of pubic hair
- arterial thrombolism
- alteration of sex ratio

Follicle-stimulating hormone (FSH)

Synonyms/trade names:
- urofollitrophin
- Metrodin®
- FRG

Usage:
- ovulation induction
- *in vitro* fertilization

Adverse effects (known or suspect):
- carcinogenicity
- ovarian hyperstimulation syndrome
- thromboembolism
- ovarian enlargement
- ovarian cysts
- pain at site of injection
- fever and chills
- skin rash or hives
- breast tenderness
- nausea, vomiting, diarrhea
- multiple births
- adverse effects similar to hMG

Human menopausal gonadotropin (hMG)

Chemical Abstracts Service Registry Number: 9002-68-0

Synonyms/trade names:
:menotropin or menotrophin
:3-hydroxy-3-methylpentanedioic acid
:3-hydroxy-3 methylglutaric acid
:meglutol
:dicrotalic acid
:medroglutaric acid
:HMGA
:CB-337
:lipoglutaren
:mevalon
:Pergonal®
:Fertinorm
:Human Pituitary Gonadotropin
:Humegon
:Inductor
:Neo-Pergonal

:Pregova (menotropin)

Usage:

- — ovulation induction
- — spermatogenesis

Adverse effects (known or suspect):

- — ovarian hyperstimulation syndrome
- — pulmonary and vascular complications
- — multiple births
- — carcinogenesis and mutagenesis
- — haemoperitoneum
- — ovarian enlargement
- — ovarian cysts
- — abdominal pain
- — allergic sensitivity
- — gastrointestinal symptoms
- — pain at site of injection
- — body rashes
- — dizziness, tachycardia, dyspnea, tachypnea
- — ectopic pregnancy
- — congenital abnormalities
- — gynaecomastia
- — erythrocytosis

Appendix 2

Sample Questionnaire

Ovulation Induction Outcome Survey
(University of Calgary)

1. What is the total number of new couples seen in your clinic per year?

0 - 100	( )
101 - 200	( )
201 - 300	( )
301 - 400	( )
401 - 500	( )
501 - 600	( )
601 - 700	( )
701 - 800	( )
801 - 900	( )
901 - 1 000	( )
> 1 000	( )

2. How many of your patients are treated with clomiphene citrate?

0 - 100	( )
101 - 200	( )
201 - 300	( )
301 - 400	( )
401 - 500	( )
501 - 600	( )
601 - 700	( )
701 - 800	( )
801 - 900	( )
901 - 1 000	( )
> 1 000	( )

3. How many of your patients are treated with human menopausal gonadotropin?

0 - 100	( )
101 - 200	( )
201 - 300	( )
301 - 400	( )
401 - 500	( )
501 - 600	( )
601 - 700	( )
701 - 800	( )
801 - 900	( )
901 - 1 000	( )
> 1 000	( )

4. What is your estimate of the following complications of clomiphene citrate?

	PERCENT								
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
ovarian pain										
ovarian cysts										
hyperstimulation										
pregnancy										

twins

triplets

abortion

congenital
malformations
- anencephaly

- spina bifida

- other

5. What is your estimate of the following complications of human menopausal gonadotropin (for ovulation induction not *in vitro* fertilization)?

	PERCENT								
	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
ovarian pain										
ovarian cysts										
hyperstimulation										
pregnancy										
twins										
triplets										
abortion										
congenital										

malformations
- anencephaly

- spina bifida

- other

6. Are you aware of one or more case reports, in your clinic, in which there is an association of ovulation induction and ovarian cancer? Please give a brief case summary including **age, time relationship, total dose of drugs**, and **type of ovarian cancer**.

7. Do you have any other observations to make regarding the adverse outcomes of ovulation induction?

Appendix 3

Outcomes

Below are the values or codes assigned to the outcome variables defining specific adverse outcomes and the number of articles in the data base in which the specific outcome was reported. The first two digits refer to specific conditions or observations. Conditions related to cancer were assigned digits 50 to 59. When an article reported an adverse outcome or deterioration of a condition, the outcome variable was assigned a positive code. Improvements in a condition were indicated by a negative code (e.g., lessening of abdominal pain is -0201) in the data base, and in this table the total number of occurrences of the specific negative codes is presented. Some rates were not assigned a direction in their code, and for those a negative code refers to a reduced rate. However, many codes for rates were assigned a direction (indicating a clear adverse effect) and a negative code was used to indicate the opposite direction.

		Total number of occurrences	
		Positive	Negative
0200	**Gastrointestinal**		
01	abdominal pain	8	0
02	nausea, vomiting	17	0
03	diarrhea	1	0
04	constipation	3	0
05	anorexia	1	0
06	micturition	6	0
08	bloating with pain	3	0
0300	**Respiratory**		
01	pulmonary distress	7	0
02	pulmonary embolism/edema	1	0
06	hydrothorax	1	0
08	pleural effusion	1	0
0400	**Cardiovascular**		
01	thromboembolism, not otherwise classified	2	0
08	thrombophlebitis	2	0
12	heart malformation, not otherwise classified	1	0
15	thrombosis	2	0
16	occlusion of cerebral artery	1	0
0500	**Nervous system**		
01	dizziness	9	0
02	vertigo	1	0
03	insomnia	4	0
04	depression	9	0
05	headache	11	0
06	sleep disorders	1	0
08	psychosis	5	0
10	convulsions/seizure	1	1
16	hyperexcitability	1	0
18	shock	1	0
19	memory loss	1	0
28	general neurologic symptoms	1	0
29	behavioural changes, not otherwise classified	1	0
31	epilepsy (seizures) increase	1	2
32	fatigue	2	0
34	behaviour change	1	0
37	emotional change	1	0
38	social introversion	1	0
39	semantic differential	1	0

		Total number of occurrences	
		Positive	Negative
0600	**Liver**		
01	abnormal liver function test	3	0
30	degenerative change in liver	3	0
50	tumour induction	2	0
0700	**Kidney**		
01	kidney failure	2	0
0800	**Skin**		
01	rash	2	0
02	mottling	1	0
03	alopecia	2	0
10	bullae/urticaria/allergic dermatitis	4	0
11	hirsutism	1	0
13	cutaneous annular erythema/photosensitivity	1	0
17	hair loss	1	0
18	pruritus	1	0
30	dermatologic deterioration, not otherwise classified	2	0
0900	**Haematological/lymphatic/hormonal**		
25	hyperbilirubinaemia	2	0
26	anaemia, not otherwise classified	1	0
1000	**Special senses**		
01	blurring vision	6	0
02	cataracts	2	0
03	scotomas	2	0
04	visual side-effects, not otherwise classified	16	0
05	optic neuropathy	1	0
1200	**Endocrine**		
03	haemorrhage into pituitary gland	1	0
1500	**Urogenital — female**		
01	ovarian enlargement	39	1
02	ovarian hyperstimulation	176	5
03	pelvic pain/ovarian pain	17	0
04	menopausal symptoms	2	0
05	premenstrual symptoms	2	0
06	ovarian cysts/polycystic ovary	74	0
08	haemoperitoneum	3	0

		Total number of occurrences	
		Positive	Negative
1500	**Urogenital — female** (*cont'd*)		
09	luteal phase defect	4	0
11	anovulation	8	0
12	oligo-ovulation	2	0
15	delayed deficient endometrial maturation	3	1
16	tubal disorder	9	0
18	uterine hyperplasia	1	1
21	follicular growth delayed	2	0
22	oligomenorrhoea/amenorrhoea	7	0
24	follicular cysts	1	0
38	ovarian torsion	9	0
41	partial ovariectomy	1	0
45	decreased endometrial thickness	1	0
46	uterus bicornis unicollis	1	0
47	adenomatous hyperplasia	1	0
49	dysfunctional bleeding	2	0
50	ovarian tumours/carcinoma	9	0
51	endometrial carcinoma	2	0
53	uterine tumours	2	0
54	choriocarcinoma	1	0
60	endometrial calcification	1	0
61	urinary tract infection	2	0
1600	**Breast**		
01	breast tenderness	12	0
05	microcystic	1	0
06	macrocystic	1	0
50	breast neoplasms	3	0
1700	**Pregnancy**		
01	multiple ovulations/ superfecundation	3	0
02	superfetation	1	0
03	multiple birth, not otherwise classified	143	2
04	premature birth	55	0
05	spontaneous abortion/pregnancy loss, not otherwise classified	304	12
06	ectopic/extrauterine pregnancy	127	3
07	stillbirth/neonatal death/fetus not viable	27	0
08	Caesarian	36	0

		Total number of occurrences	
		Positive	Negative
1700	**Pregnancy** (*cont'd*)		
09	hypertension	8	0
10	intrauterine growth retardation	7	0
11	hydatidiform mole/molar pregnancy	24	0
14	toxaemia/pre-eclampsia	12	0
15	complications of pregnancy	6	0
16	complications of delivery	3	1
17	decreased birth weight	12	0
18	heterotopic pregnancy	37	0
19	multiple birth — twins	125	0
20	multiple birth — triplets	85	0
21	multiple birth — quadruplets	35	0
22	multiple birth — quintuplets or higher	25	0
23	multiple birth — triplets or higher	1	0
24	selective abortion/selective reduction	17	0
25	diagnostic delay of ectopic	15	0
27	inappropriate diagnosis of heterotopic	3	0
28	breech	3	0
29	vaginal bleeding/trimester	4	0
30	resorption or disappearance	3	0
31	triple ectopic	1	0
32	septic abortion	1	0
33	chorioamnionitis	1	0
34	fetal wastage (abortion, stillbirth, ectopic, or blighted ovum)	6	0
35	hydraminios/polyhydraminios	2	0
36	abruptio placentae/abruption	1	0
37	morning sickness	2	0
38	gestational diabetes mellitus	2	0
39	premature rupture of membranes	1	0
42	change in sex ratio	52	9
61	induced labour	1	0
1900	**Second generations**		
01	neural tube defects, not otherwise classified	28	0
02	Down syndrome	3	0
03	hypospadias	2	0
04	hydrocephalus	3	0

		Total number of occurrences	
		Positive	Negative
1900	**Second generations** (*cont'd*)		
10	clubfoot	1	0
12	cleft lip and palate	5	0
13	fetal ovarian dysplasia/ovarian enlargement/ovarian cysts	1	0
17	spina bifida	2	0
19	transposition of large vessels	2	0
20	meningomyelocele	1	0
21	microcephaly	2	0
22	anencephaly	9	0
23	cardiovascular system, not otherwise classified	6	0
24	delayed development in childhood	4	0
30	reproductive tract anomalies	1	0
35	ectopic urinary bladder	1	0
36	acrania	2	0
38	organ defects general	1	0
39	chromosome abnormality, not otherwise classified	5	0
40	increased rate of malformation	69	0
41	increased rate of perinatal mortality	2	0
42	increased rate of malformation (minor)	4	0
44	normal birth and development	1	0
45	hypsarrhythmia	1	0
46	digits abnormal	1	0
47	megacystic-microcolon-intestinal hypoperistalsis	1	0
48	undescended testes	2	0
50	increased rate of childhood cancer	1	0
52	hepatoblastoma/liver cancer	1	0
54	neuroblastoma	1	0
55	brain tumour	1	0
56	malignant lymphoma	1	0
57	reticuloendothelial tumour	1	0
60	heart anomalies	4	0
61	delayed mental/social development	1	0
62	retinopathy/visual defects	1	0
2000	**Miscellaneous effects**		
01	abdominal distention	8	0
03	ascites	4	0
04	weight gain	6	0
05	weight loss	2	0

		Total number of occurrences	
		Positive	Negative
2000	**Miscellaneous effects** (*cont'd*)		
06	decreased libido	2	0
07	increased libido	2	0
08	vasomotor symptoms (hot flashes)	37	0
16	salpingo-oophorectomy	1	0
17	induration at injection site	1	0
18	general side-effects	6	0
19	heavier menses	1	0
20	previous hMG-induced pregnancy	1	0
2100	***In vitro* fertilization**		
01	degeneration of ova	1	0
02	delayed oocyte maturation	1	1
03	retarded transformation-blastocyte	2	0
04	chromosomal abnormality egg/oocyte	7	0
05	chromosomal abnormality embryos	7	0
06	sperm penetration (decrease)	1	0
09	oocyte quality (decrease)	2	0
10	embryo development (decrease)	1	0
11	fractured zona/oocyte	1	0
40	cleavage rate	6	2
43	rate of degeneration of ova	1	1
44	rate of recovery of oocytes	5	1
45	number of embryos per cycle	1	0
46	rate of triploidy/polypronuclear embryos	0	1
47	decrease rate of implantation (nidation)	2	0
48	number of embryos per oocyte	1	0
2200	**Pretreatment conditions or conditions not found above**		
02	enrolled in IVF program	224	0
03	enrolled in IUI program	10	0
04	donor insemination program	7	0
05	neurofibromatosis	2	0
06	endometriosis	4	0
07	ovulation induction in GIFT	38	0
08	ovulation induction, not otherwise classified	394	0
09	castration	2	0
10	previous episodes of hyperstimulation	1	0
11	pregnancy	7	0
12	birth/all birth	5	0
14	hyperprolactinaemia	1	0

		Total number of occurrences	
		Positive	Negative
2200	**Pretreatment conditions or conditions not found above** (*cont'd*)		
15	spontaneous pregnancy	7	0
16	previous episodes of spontaneous abortion	2	0
17	cryptorchidism	1	0
18	zygote intrafallopian transfer program	3	0
19	unexplained infertility	1	0
30	cell deterioration	2	0
51	childhood malignant disease	1	0
9900	**Other**		
96	controls — normal birth	5	0
97	unexposed control group	9	0
98	non-diseased control group	2	0

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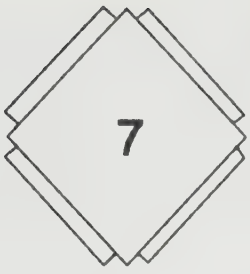
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Methodological Challenges in Evaluating a New and Evolving Technology: The Case of *In Vitro* Fertilization

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Executive Summary

This study examines some of the methodological issues considered and the challenges encountered in an evaluation of the *in vitro* fertilization (IVF) program at Chedoke-McMaster Hospital in Hamilton, Ontario. Describing the ethical and study design issues that were confronted, the authors stress the importance of evaluating a technology before it is disseminated, by means of a randomized controlled trial (RCT). Because IVF was largely publicly funded and made available on the basis of anecdotal evidence of its efficacy, a conclusive RCT evaluation of IVF treatment compared with other or conventional fertility treatment could not be conducted, since those seeking and eligible for treatment could not be denied it. The researchers therefore adopted a quasi-RCT research design, whereby one group of patients was assigned to immediate IVF treatment (the experimental group) and the other was assigned to a waiting list (the control group). The researchers encountered some additional challenges that were a result of this research design: the six-month waiting period for the control group meant that the number of cycles observed on the experimental group was limited; there were delays in scheduling treatment for the

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experimental group; and there was a sizeable proportion of drop-outs, especially in the control group.

The success of IVF can be calculated in various ways (e.g., pregnancies per patient, pregnancies per cycle initiated, or pregnancies per embryo transferred) and from the perspectives of various interest groups (research methodologists, patients, insurers/payers, and IVF advocates) that can have different views as to whether to include drop-outs, pretreatment pregnancies in the experimental group, and contaminated cases. Calculations from these different perspectives can yield different and possibly conflicting results. The authors outline the relationships among these issues.

Another challenge is that new technologies are always evolving and subject to refinement and modification. IVF is no exception; the authors list some of the changes that took place at the Chedoke-McMaster IVF clinic during the study. In addition, with almost all new technologies there is a learning curve effect where the expertise of people involved in administering the treatment is constantly developing. The challenge thus arises of when to evaluate; this involves a trade-off between evaluating a technology before it is fully disseminated and giving it an adequate chance to develop.

The authors also discuss the implications and relevance of these issues and this study design for other studies. They conclude that while some of the techniques and methods described here are applicable to other health care programs, all programs have specific challenges and issues and have to be evaluated accordingly.

Introduction

In vitro fertilization (IVF) is a relatively new and constantly evolving technology. It is not surprising, therefore, that reports of success following IVF treatment have shown a wide range in the literature. A large portion of this variation can be attributed to differences in how success is calculated. Definitions of success vary, and may be calculated on a per patient basis; on the basis of cycles initiated or cycles completed; on a per embryo transferred or per cleaved embryo basis; or may be calculated on the basis of only a narrowly defined group of patients (e.g., those with tubal factor infertility). The variation in success rates in other studies is due to: differences in treatment protocols and techniques; drugs and supplies used; patient compliance; and differences in the expertise and experience of staff, nurses, technicians, and physicians involved in IVF treatment. The evaluation of a specific IVF program, therefore, is confounded by many variables, including: different definitions of success; the expertise of the staff; and changes in technology and how it is applied.

We evaluated the IVF program at Chedoke-McMaster Hospital in Hamilton, Ontario over the period February 1987 to April 1990. In this report we discuss some of the methodological issues and challenges associated with this evaluation. We then draw conclusions regarding the

relevance of these issues and the methods for evaluating other interventions and technologies. Since many reproductive techniques are comparatively new and evolving, this report is particularly relevant for interpreting the evaluations of these technologies and will assist researchers in the design of future studies.

Evaluating IVF: Methodological Challenges and Issues

The principal methodological challenges and issues encountered in the study of IVF can be summarized into five broad categories: research ethics and study design; secondary research questions; variables used to calculate outcomes; the constantly evolving nature of the technology; and the "learning curve effect" of IVF treatment.

Research Ethics and the Quasi-RCT Research Design

Researchers and policy makers stress the importance of evaluating technology before it is disseminated. Evidence that a procedure or technology works under ideal experimental conditions does not mean that it is efficacious when compared with other types of treatment, or effective or efficient when implemented in clinical settings. Ideally, randomized controlled trials (RCTs) should be executed to answer these important questions. Once a procedure or technology is in a clinical setting, however, public opinion, lobby group pressures, and ethical issues associated with denying the treatment all contribute to the difficulty of further evaluating it.

Our analysis of an existing IVF program provides support for the argument in favour of rigorous evaluations of technology before they are disseminated. Evidence that IVF treatment can work had been established for more than 10 years before the start of the study. Based on anecdotal evidence of its efficacy compared with no fertility treatment, (i.e., that it apparently works better), the Province of Ontario began to fund the procedure. This was without evidence of the procedure's efficacy (i.e., whether it works better under ideal experimental conditions) compared with other fertility treatment, its effectiveness (i.e., whether it works better in real clinical settings) compared with other fertility treatment, or its efficiency (i.e., whether it works better than other programs in terms of benefits and costs). The anecdotal nature of the evidence of the efficacy of IVF treatment, combined with public funding and therefore public access, meant it was difficult and unethical to deny the procedure to those seeking and eligible for treatment. For these reasons it was not possible to conduct a conclusive RCT evaluation of IVF treatment versus conventional or other forms of fertility treatment.

Although less preferred, case-control (i.e., matching two cohorts) or within-cohort before-and-after study designs could be used to evaluate

technologies under these circumstances. Case-control studies require a matching of cohorts for comparison. For example, IVF patients could be matched with patients in another geographical area who have access to conventional fertility treatment but not IVF. Alternatively, IVF patients could be compared with other patients in the same geographical area who have similar fertility problems. Using either approach, the success of the two groups could then be compared over time. The main challenge for case-control studies is finding a cohort that is an exact match for the experimental group at the beginning of the study and over time. There may be fundamental differences between cohorts across geographical areas at the start of the study that could have a differential impact on the outcomes of the evaluation. Similarly, there may be variables like stress and lifestyle or environmental factors that have a differential impact on the outcomes for the two cohorts. For these reasons, case-control studies are not only difficult to implement but also involve uncertainty as to whether important variables were overlooked and not controlled in the evaluation.

The within-cohort before-and-after study design uses the same patients, thereby attempting to control some of the variables that may differ among individuals in the same geographical area or across geographical areas. The patients are observed during a pre-treatment period and a post-treatment period in an attempt to measure the success of the treatment alone. The problem with the before-and-after study design is that variables that may influence success over time (e.g., age, duration of infertility, stress, lifestyle, and environmental factors) are difficult — if not impossible — to control, so better or worse outcomes may not be attributable to the intervention or treatment alone.

We decided, therefore, to use a quasi-RCT research design (see Appendix 1). Half the couples who enrolled in Chedoke-McMaster's IVF program were assigned to immediate IVF treatment (the experimental group) and half were assigned to a waiting list (the control group). Although IVF treatment could be delayed, on ethical grounds it could not be denied to eligible patients. There was also the ethical question of how long treatment could be delayed for research purposes. Since a six-month waiting period would reasonably have been expected in the absence of the study, a waiting period of at least six months was identified for study participants assigned to the waiting or control group. What happened to patients receiving conventional fertility treatment during this six-month waiting period was then compared with successful outcomes for patients assigned to immediate IVF treatment. Although the control patients were not true control patients because they knew they would eventually receive IVF treatment, this quasi-RCT research design allowed us to control many external variables or influences, thus overcoming many of the problems associated with the case-control and before-and-after research designs.

Although controlling for many external variables, this quasi-RCT research design created three additional challenges. First, since the waiting period for the control group was only six months, the number of IVF

treatment cycles that could be observed on the experimental-group patients was limited. Second, the waiting period affected the overall length of observation for the two groups. And finally, the crossover design of the study (i.e., patients initially assigned to the control group eventually 'crossed over' and received IVF treatment) created unanticipated scheduling delays in the clinic for experimental-group patients.

Number of Cycles/Months of Observation

The short waiting period for control-group patients and the matched observation time for experimental-group patients meant that only a limited number of IVF treatment cycles could be observed for each experimental-group patient. In addition, the crossover design of the study meant that all the control-group couples would eventually receive treatment in the same clinic. This put additional pressure on clinic management and scheduling and further restricted the number of treatment cycles that could be initiated on couples assigned directly to the experimental group. The result of these delays is that an average of only 2.05 IVF treatment cycles were initiated on experimental-group patients.

The significance of a limited number of IVF treatment cycles depends on the cumulative success of IVF treatment and the extent to which overall pregnancy rates are cumulative for patients with fertility problems. If IVF success rates are cumulative up to a certain number of attempts, and if this number of attempts is more than two cycles, on average, per patient, then the results of this specific evaluation of IVF may not have captured the long-run benefits of IVF treatment. Although the clinical results of the study showed no significant differences in pregnancy or live births rates between "IVF Treatment" and "No IVF Treatment" for the observation period, it is possible that IVF treatment would result in higher pregnancy or live birth rates over a longer observation period. Since the observation period and the number of cycles that could be observed was limited, this hypothesis could not be tested.

Different Periods of Observation

Because of drop-outs, research studies are subject to different periods of observation for each patient and therefore for each group. With a randomized controlled research design and with a large enough sample of patients, drop-outs, and therefore periods of observation for the two groups, should balance out. With a quasi-RCT research design, however, there is the potential for a large number of drop-outs, particularly among waiting or control-group patients. Since these patients have to wait much longer to receive treatment, they may get tired of waiting and decide not to have children, to adopt a child, or to seek IVF treatment at another centre within or outside the province. In the evaluation of Chedoke-McMaster's IVF program, 45 of the total of 205 experimental-group patients (22 percent) and 61 of the 194 control-group patients (31 percent) dropped out of the study. The reasons for dropping out for both groups are presented in Table 1. Of particular interest is the large number of patients who were lost to

contact or who received treatment elsewhere. Data for these patients should be included in an intention-to-treat analysis. However, as was the case for the present study, obtaining data for these patients may be difficult or impossible. With the quasi-RCT research design, there is a potential trade-off between the observation period and the risk of a higher number of drop-outs from the waiting group.

Table 1. Reasons for Dropping Out

	Experimental group	Control group
Lost to contact	15	31
Treatment elsewhere	5	10
Alternative treatment	2	2
Ambivalent toward IVF	9	11
Health	6	2
Marital separation	2	2
Religious/financial concerns	3	0
Adopted	3	3
Total	45	61

IVF Treatment Delays

The third challenge created by the quasi-RCT design of the study arose because of the additional pressure on clinic management and scheduling as a result of the additional patient volume that was created by obligations with the crossover design of the study. Patients assigned to the experimental group were supposed to receive IVF treatment within four months of randomization. The actual mean time until the first treatment cycle was eight months. Although this unanticipated delay did not create a problem for the methods used for analyzing the data, it did create other problems. First, it probably had an impact on the drop-out rate for the experimental group (see Table 1). Second, a large number of the 33 pregnancies in the experimental group (13, or 39%) occurred before IVF treatment was initiated. Because of these pre-treatment pregnancies, the interesting question arises of whether these pregnancies should be attributed to the intervention. (The issue of which variables to include in the calculation of success rates is discussed later.)

Secondary Research Questions

Most clinical studies have one or two primary questions or hypotheses. There are usually also a number of secondary or alternative questions that are important to fully evaluating a program or technology. Funding

agencies are typically unwilling to fund projects that address these secondary questions because of the disproportionately higher cost and longer study length involved. The sample sizes calculated for the primary questions or hypotheses are typically inadequate to address these important secondary questions. In the case of IVF, two important secondary questions could not be addressed with the sample sizes calculated for the primary research questions: pregnancy and live birth rates by diagnostic category of infertility; and the long-run health outcomes of the babies born.

Analysis by Diagnostic Category of Infertility

A separate analysis by diagnostic category of infertility could not be conducted because of inadequate sample size (i.e., there was inadequate statistical power to detect differences in success rates by category of infertility). This is a potential concern for IVF since it was initially intended for tubal factor infertility. Although its use was eventually expanded to other forms of infertility, including idiopathic (unexplained) and male sperm factors it is likely to be more beneficial to women with tubal factor infertility. Although IVF was shown overall not to be effective or to be of limited effectiveness compared with conventional fertility treatment, its effectiveness by diagnostic category of infertility could not be tested.

Long-Run Health Outcomes of Babies Born

Additional analyses comparing the long-run health outcomes of the babies born through IVF with those of babies born through natural conception could not be conducted because of inadequate sample size and power to detect a difference. This issue is also a potential concern for IVF treatment because of the higher incidence of multiple births and therefore the higher health risk to the babies associated with the procedure. Although there are well-established instruments for measuring the development and health of children, these instruments were not used because of the small number of babies born during the study period.

Calculating the Outcomes: Which Variables to Include?

Definitions of IVF success rates in the literature vary widely from success calculated on a per patient basis or on a per cycle basis, to success calculated on a per embryo transferred or per cleaved embryo basis. Each of these approaches yields different results, and because each calculation answers slightly different questions, the calculations may not be of equal concern to various interest groups. In the case of IVF, for example, four distinct interest groups can be identified: research methodologists; patients; IVF advocates or stakeholders; and insurers/payers. Each might hold different views about the importance or appropriateness of the different calculations of success. One possible mapping of the relationships between interest groups and the choice of preferred outcome measures is presented in Table 2.

Table 2. Possible Relationships Between Interest Groups and the Choice of Preferred Outcome Measures

Interest group	Pregnancies per patient	Pregnancies per cycle initiated	Pregnancies per cycle completed	Pregnancies per embryo transferred	Pregnancies per cleaved embryo
Research methodologist	yes	yes	no	no	no
Patient	yes	yes	?	no	no
Insurer/ payer	?	yes	no	no	no
IVF advocate or stakeholder	yes	no	yes	yes	yes

The research methodologist might advocate that success rates only be calculated on per patient or per cycle initiated bases. These are the only calculations that are consistent with an intention-to-treat methodological perspective. The patient might also be interested in these two calculations as they are the most meaningful from his or her perspective. The insurer/ payer is likely to be interested in success rates calculated on a per cycle initiated basis, but might also be interested in those calculated on a per patient basis. The IVF advocate or stakeholder, however, is likely to be interested in a more narrow definition of success, such as per embryo transferred, per cleaved embryo, or per cycle completed. These calculations tend to make the success of treatment look more favourable because failures up to these points are, by definition, excluded. This is one of the main reasons why those responsible for delivering care should not be principally involved in its evaluation. For similar reasons, the IVF advocate is also less inclined to use all cycles initiated (which includes incomplete cycles) in reporting success.

In addition to different perspectives on calculating and reporting outcomes, the interest groups might also have conflicting opinions as to which variables should be included. In this study of IVF, three variables had an impact on the calculation of success: drop-outs; pre-treatment pregnancies in the experimental group; and contaminated cases (i.e., experimental patients still awaiting treatment at the end of the study). One possible mapping of the relationships between the interest groups and these three variables is presented in Table 3.

Table 3. Possible Relationships Between Interest Group and Variables to Include in the Calculation of Outcomes

Interest group	Drop-outs	Pre-treatment pregnancies	Contaminated cases
Research methodologist	yes	yes	yes
Patient	no	yes	no
Insurer/payer	no	no	no
IVF advocate or stakeholder	no	yes	no

From an intention-to-treat perspective, the research methodologist would advocate that drop-outs, pre-treatment pregnancies, and contaminated cases all be included in the analysis. The patient may feel that drop-outs and contaminated cases should not be included since these calculations would not represent their "true" chance of becoming pregnant if they "stuck it out." Since none of the variables in Table 3 have direct implications for cost to the insurer/payer, the insurer/payer might prefer calculations that exclude all three variables. And finally, the IVF advocate may prefer to include pre-treatment pregnancies but exclude drop-outs and contaminated cases, since this calculation is the most favourable toward IVF treatment.

Although there will be many opinions regarding the relationships between interest groups and the variables used for calculating outcomes, Tables 2 and 3 highlight the point that success rates for IVF can be calculated in a number of ways that yield very different and potentially conflicting results. It is important, therefore, to specify and justify the variables and method(s) of calculation used. These decisions have implications both for reporting the results and for the methods used to collect and analyze the data.

The Constantly Evolving Nature of IVF Technology

Another problem in evaluating a relatively new procedure or technique is that the technology is often in the developmental or experimental stage, and refinements and modifications to protocols and treatment methods are inevitable. Chedoke-McMaster's IVF program underwent numerous changes over the three-year study period from February 1987 to April 1990. Some of these changes were minor changes to protocols or techniques, while others were more substantial. The more significant include: changes to induction protocol in April, August, and October of 1987, January and October of 1988, and May, June, July, and October of 1989; improvements in quality control measures throughout the study period; the change from retrievals by laparoscopy to ultrasound retrievals

between January and October 1988; less aggressive methods of sperm preparation during 1987; the change from large culture dishes to NUNC wells in June 1989; and, perhaps most significant, the change from double distilled water to Barnstead water purification in October 1988.

Appendix 2 summarizes these and other changes. Although Appendix 2 only classifies the changes crudely as major and minor, it indicates the total number that occurred and highlights the potential problem of evaluating this constantly evolving technology. The specific impact that each of these changes had on the success of IVF treatment is uncertain, however, as each change would in itself require an individual study.

The "Learning Curve Effect" of IVF Treatment

The expertise and experience of staff, nurses, technicians, and physicians involved in IVF treatment reflect and are also a major impetus behind the implementation of these changes in protocol, equipment, and technology. With most technology, the skills and expertise of the staff continue to improve with time (at least up to a point). The so-called "learning curve effect" is common to almost all new technology and even the most established technologies. Since evaluating a program too early might bias the evaluation unfairly against the intervention, the problem arose of deciding the right time to evaluate the IVF program.

As shown in Appendix 3, the annual number of cycles initiated in Chedoke-McMaster's IVF clinic continuously increased over the period 1985-1990. Although not measured and extremely difficult to prove, it was hypothesized that the skills and expertise of the staff involved in IVF treatment would continue to improve over this period and that a large portion of the improvement would occur during the first few years of operation. It was believed that starting the study in 1987, two years after treatments first began in the clinic, was optimal, since the delay would capture most of the "learning curve effect." In the absence of more rigorous information, estimates of the "right time to evaluate" were made with physicians and staff working in the clinic. Whether this was the optimal time or whether an optimal time could have been identified at all is uncertain, given the number of changes that took place in the clinic over the study period.

Discussion and Relevance for Other Evaluations

Quasi-RCT Research Design

Under ideal research conditions, RCTs should be used to evaluate new or existing technologies. However, in situations where they cannot be used — for ethical or other reasons — the quasi-RCT research design that we used to evaluate IVF may be preferred to case-control or before-and-after

study designs. This research design has many of the advantages of the RCT and has wide applicability for evaluations of other interventions. However, one of the main, and as yet unanswered questions is, "how long can treatment be delayed before the delay itself is considered unethical?" We used a six-month period on the grounds that the waiting period in the absence of the trial would probably have been six months anyway. But would it have been unethical to delay treatment 12 or 18 months? This ethical question is beyond the scope of the present paper; however, it is of vital importance for the wide applicability of the quasi-RCT research design. A longer waiting period would have allowed us to evaluate more IVF treatment cycles per patient and therefore address concerns over whether IVF had been given an adequate chance.

For evaluations of interventions that can be tried only once or where the benefit of subsequent attempts is negligible (i.e., hit-or-miss interventions), this issue of the delay is not as large a concern. For interventions that can be tried more than once, repeatedly or continuously, however, and where there are potential benefits of doing so, the ethical question of how long treatment can be delayed becomes a major concern. The issue is also important for interventions that require longer-term treatment and those where the benefits of treatment occur and are measured some time into the future. In both of these situations a much longer waiting period for the control group may be required. An argument can be made, on ethical grounds, that the quasi-RCT research design may be inappropriate for these evaluations and that a different one should be used.

It can be also be argued that control- or waiting-group patients in the quasi-RCT research design are not true control patients, since they know they will eventually receive treatment. This is potentially a concern for evaluations of programs such as IVF where stress or pressure may be important factors influencing the outcomes. It has long been suspected that stress is a major risk factor associated with idiopathic or unexplained infertility. In other words, perhaps the control-group pregnancy rates were influenced by the reduction in stress they experienced as a result of knowing that they would soon receive state-of-the-art treatment. Since IVF patients usually have a long history of infertility, and since other treatments — including stress reduction — have likely already been explored, it is unlikely that this is a major concern in the evaluation of IVF. Nevertheless, for evaluations of interventions where stress or pressure may be important factors, the quasi-RCT research design should be used with caution.

With a quasi-RCT research design there is a potential trade-off between the observation period and the risk of a higher number of drop-outs in the waiting or control group. This trade-off is more likely to be an issue for non-life-threatening and quality-of-life enhancing interventions than it is for life-threatening interventions. For life-threatening interventions, the potential for the two groups to have different periods of

observation occurs naturally because of the risk of death. It should be noted that there are statistical methods for handling variable periods of observation, such as truncating the length of observation, analyzing the data on a per week or per month at-risk basis, and the preferred approach, survival analysis. The main concern arising from the trade-off between the observation period and the risk of a higher number of drop-outs in the waiting or control group is that the number of patients left for which observational data are available may be less than the sample size that was calculated to detect significant differences between the two groups. When using the quasi-RCT research design, techniques such as over-sampling in the waiting or control group should be used to anticipate the possibility of higher drop-out rates.

Finally, although the ethical question of how long treatment can be delayed is beyond the scope of the present paper, it should be noted that this question is rooted at the individual patient level. At a more collective or societal level, additional ethical issues come into play which may be at odds with ethical issues at the individual patient level. In the case of IVF, evidence of the procedures's efficacy or effectiveness compared to conventional treatment had not been proven previously. From society's perspective (the collective level) it can be argued that it may be unethical to use public resources to fund a procedure whose efficacy and effectiveness is not known. By devoting public resources to IVF, resources are denied from other programs and services whose efficacy and effectiveness may be well established. Although the quasi-RCT research design may be questionable on ethical grounds at the individual patient level (i.e., since treatment is delayed for some), it may be ethical at the societal or collective level if the procedure has unknown efficacy or effectiveness.

Secondary Research Questions

For evaluations of programs where there are important secondary research questions, it is essential to convince funding agencies of their significance, or more importantly, of the consequences of not addressing them. If they are not addressed, even the most conclusive and rigorous research studies can leave questions unanswered. These unanswered questions give advocates of the intervention recourse to the claim that the intervention would be beneficial to the patients who were excluded from the study or to the subgroup of patients who were not analyzed separately. Research studies may then be required to answer these secondary questions. If they are addressed initially, the duplication of time, effort, and expense can be avoided.

The Calculation of Outcomes

It is always important to calculate and report outcomes with regard to the specific questions that the study was originally designed to address.

For example, from a pure intention-to-treat perspective (i.e., that of a research methodologist), variables such as drop-outs, failed or incomplete cases, and contaminated cases are typically included in the analysis. However, from another interest group's perspective (e.g., the patient's, insurer/payer's or treatment advocate's), the inclusion of these variables is at least questionable and would most likely be considered inappropriate. Outcomes of interventions can be calculated in a number of alternative ways, and it is unlikely that any one will satisfy all interest groups (see Tables 2 and 3). It is therefore important to consider these alternative ways of calculating outcomes and to explicitly identify all research questions before a study begins.

Constantly Evolving Technology and the Learning Curve Effect: Choosing the Right Time to Evaluate

Technological advances and improvements in the experience and expertise of staff and physicians play a major role in changes to administrative policies, treatment protocols, and laboratory techniques for all new and evolving technologies. Since most new technologies are in the developmental or experimental stage, refinements and changes to protocols and policies are inevitable. These problems are compounded for prospective research studies that are relatively long or where little is known about the technology. As techniques, knowledge, skill, and expertise progress, advances are made further along the learning curve of the technology. Determining the best time to evaluate these evolving technologies usually involves a trade-off between evaluating the intervention before it is widely disseminated and giving it an adequate chance to develop. Evaluating programs near the beginning when staff and physicians are learning the most (i.e., on the steepest part of their learning curve) will likely bias the evaluation against the new technology. Waiting too long before evaluating the technology, however, creates additional problems for research study design as advocates, stakeholders, and interest groups battle to maintain or further develop the technology. In general, the evaluation should be conducted soon after the introduction of the technology, after some of the bugs are worked out but before the technology is widely disseminated.

Once an evaluation has started, it is important to control for as many changes in protocols, techniques, and policies as possible. If too many changes are introduced into the study, it will not be possible to determine afterwards whether the basic technology affected the overall results or whether one or more of the many changes were major contributors. Decisions to allow changes to be introduced into the study should be based on sound evidence of the efficacy of the changes. The decision to allow for some changes to be introduced, however, may be beyond the control of the study. It may be unethical to hold back some of the more substantial advances in the treatment.

One of the major problems created by the learning curve effect is that the evaluation of a specific program is actually an evaluation of a particular point or range along the technology's learning curve and not of the technology itself. The effect is that the evaluation may not be generalizable to similar programs at other centres or even at the same centre over time. As a result, if the technology advances fast enough, the results of specific program evaluations might be dismissed as outdated before the results of the study are disseminated. Even negative study results might be dismissed on the grounds that a lot of changes have taken place since the study. Therefore, it is important to disseminate the results of studies of new and evolving technologies as soon as possible after the studies are completed.

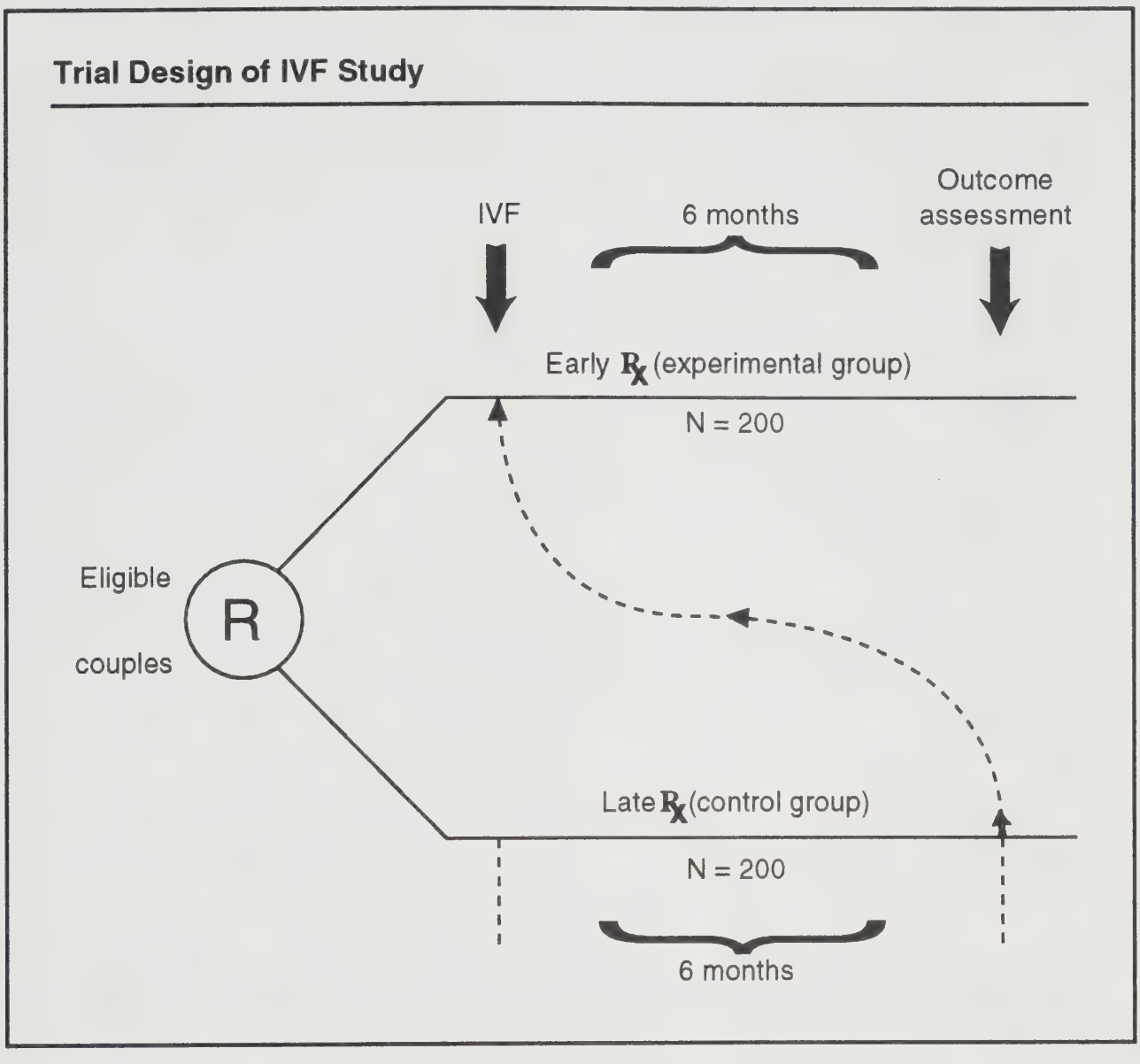
Does this mean that all new technologies have to be evaluated at several points along the learning curve or throughout the entire curve just to satisfy advocates and interest groups? If so, the evaluations will surely be never ending, as even the smallest and most insignificant changes will be deemed to make a big difference. Although it is not a comprehensive and mutually independent list, it can be argued that the existence of the following three conditions justifies further evaluation of an evolving technology:

1. initial evaluations show the technology to be equally or slightly more effective than the alternatives with which it was compared;
2. initial evaluations are conducted too early in the technology's learning curve; or
3. major breakthroughs occur in the technology that substantially alter its learning curve.

Conclusion

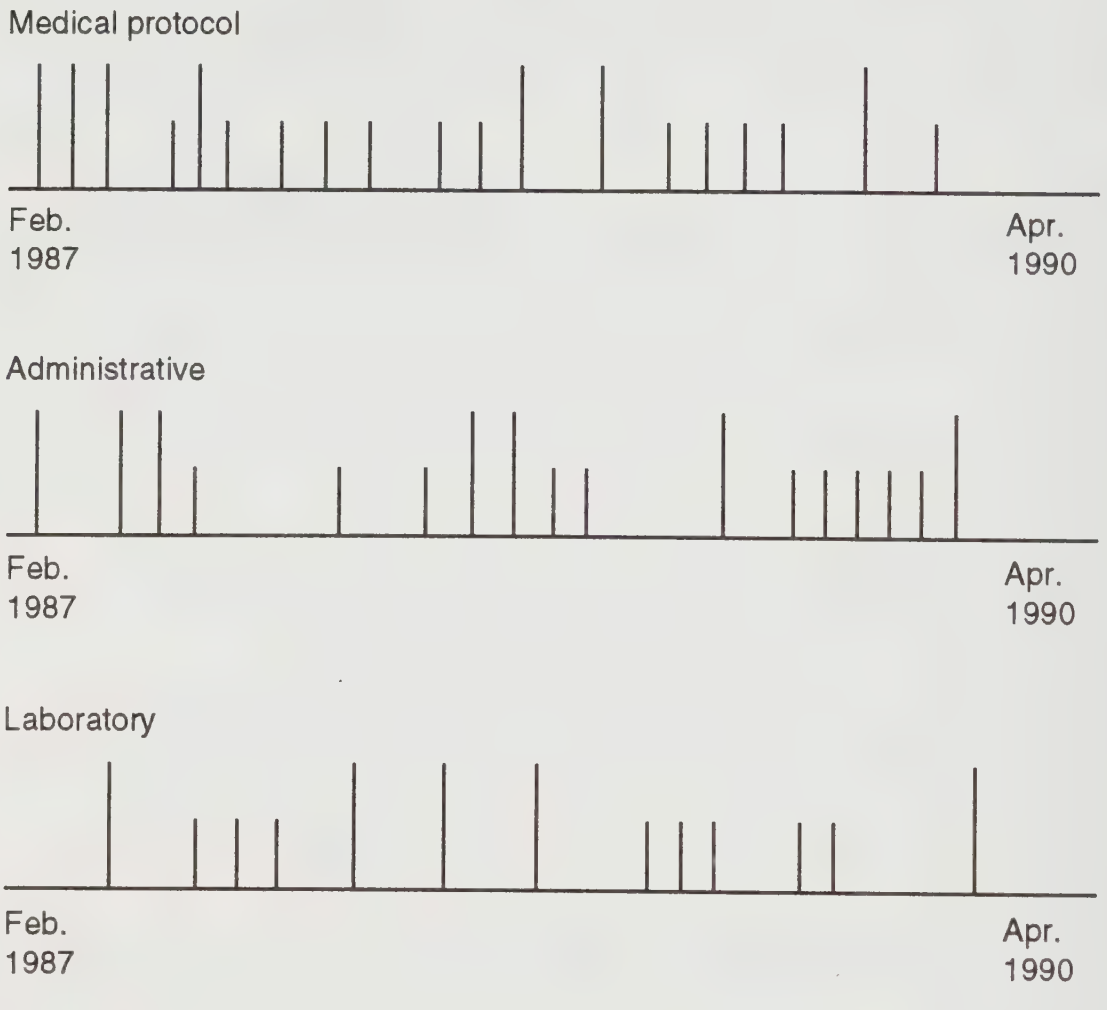
Although this report focusses on the methodological issues and challenges associated with evaluating a specific IVF program, the issues of study design, secondary research questions, the measurement of outcomes, and how to evaluate an evolving technology apply to most new and evolving technologies. Therefore, some of the techniques used to evaluate IVF are immediately generalizable to other health care programs. There are, however, issues and problems that are unique to each program, and they must be handled individually. There are no hard and fast rules that are applicable to all programs, and even the more common rules and standards are open to interpretation and debate.

Appendix 1. Trial Design of IVF Study



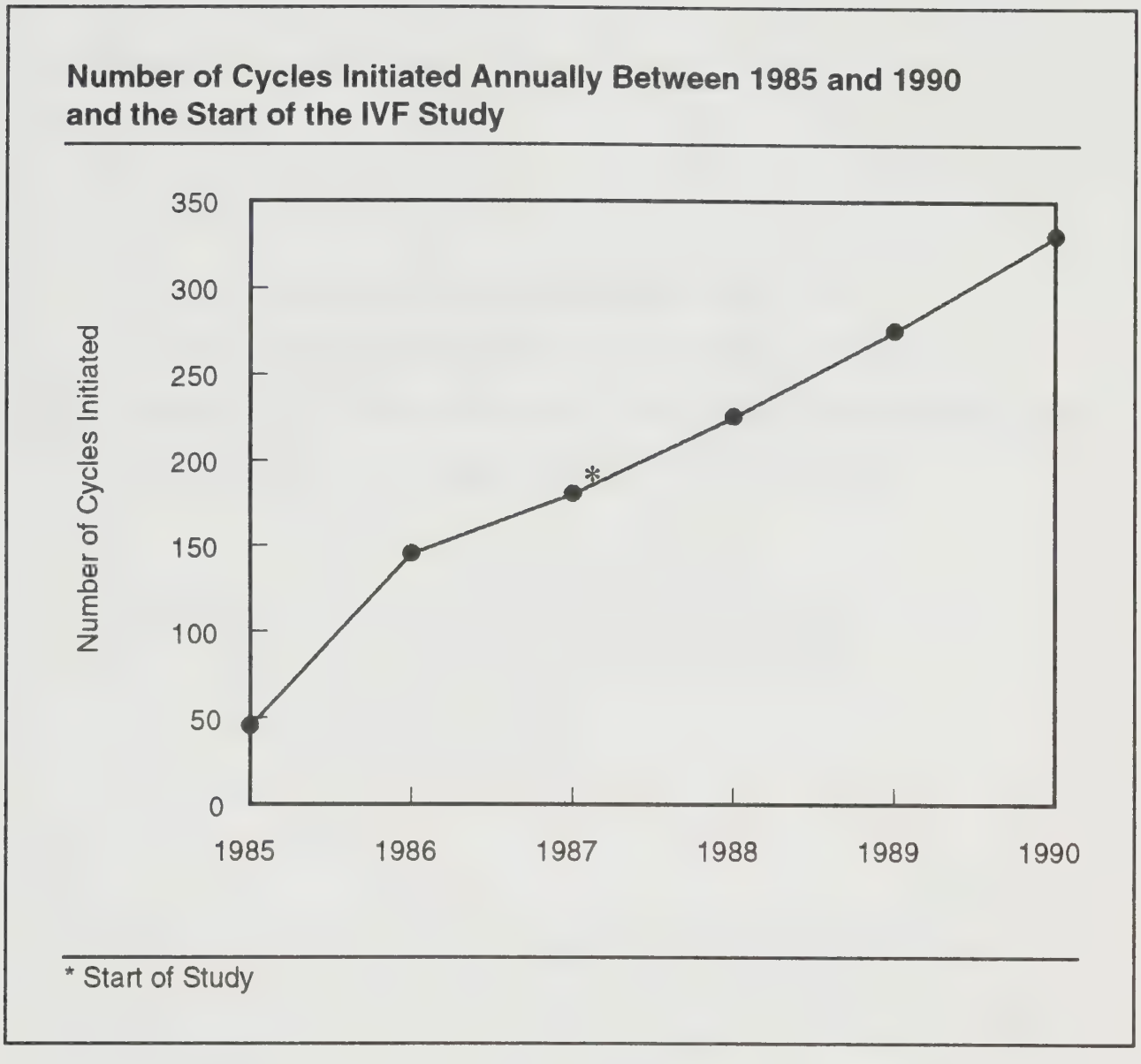
Appendix 2. Medical, Administrative, and Laboratory Changes to IVF Treatment Methods Over Study Period, 1987-1990.

Medical, Administrative, and Laboratory Changes over Study Period*



*Vertical bars indicate changes to IVF treatment methods. High vertical bars represent major changes; short vertical bars represent minor changes.

Appendix 3. Number of Cycles Initiated Annually Between 1985 and 1990 and the Start of the IVF Study



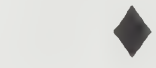
Acknowledgements

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8

Cost-Effectiveness of an *In Vitro* Fertilization Program and the Costs of Associated Hospitalizations and Other Infertility Treatments

Ron Goeree, Roberta Labelle and John Jarrell



Executive Summary

In vitro fertilization (IVF) was originally carried out on women with severe tubal disease, but its use has since been expanded to women in couples with other causes of infertility. Although there is a popular belief that the procedure has a high success rate, IVF has not been studied within a formal economic framework.

This study had three objectives: (a) to conduct a cost analysis and determine the cost-effectiveness of "IVF treatment" compared with "no IVF treatment"; (b) to estimate the costs of selected other infertility treatments, and of hospitalizations related to pregnancy; and (c) to evaluate the costs of other forms of infertility treatment. The clinic studied was the Chedoke-McMaster fertility clinic in Hamilton, Ontario. Two hundred and five infertile couples undergoing IVF were compared with 194 couples awaiting IVF treatment but receiving other infertility treatment. The couples had a variety of diagnoses. The primary outcome measure was pregnancy rates; the secondary outcome measure was delivery (parturition) and live birth rates. Single and multiple births, spontaneous abortions, ectopic pregnancies, incomplete cycles,

This paper was completed for the Royal Commission on New Reproductive Technologies in January 1992.

pre-treatment pregnancies in the experimental group, and drop-outs were also measured. The researchers identified three groups that had an interest in either excluding or including experimental-group pre-treatment pregnancies and drop-outs in the calculation of success: the patient; the insurer/payer; and society.

The cost analysis was conducted from the perspectives of the patient, the insurer/payer, and society. Costs for the control and experimental groups were collected in four main categories: direct medical costs of treatment; the cost of treating complications and side-effects of treatment; direct costs to the patient for such things as drugs and transportation; and productivity lost by patients over the course of the treatment. In addition, the researchers estimated the costs of seven other infertility treatments and four pregnancy-related types of hospitalization.

Analyzing the pregnancies, parturitions, and live birth rates, the researchers emphasize the important distinction between per-patient rates and rates per month at risk of becoming pregnant. When the rates are expressed per patient, the experimental group appeared to do better; however, the per-month-at-risk rates should be considered, because the observation period for the experimental group was significantly longer than that for the control group as a result of delays in the clinic's appointment schedule. A statistical analysis of the pregnancy, parturition, and live birth rates per month at risk revealed no overall difference between the experimental and control groups. (A cost-effectiveness analysis of particular types of infertility - for example, blocked tubes, could not be conducted due to small sample sizes.)

The cost analysis revealed that "IVF treatment" is more expensive than conventional infertility treatment or "no IVF treatment." A comparison of the pre- and post-treatment periods with the control period revealed that the incremental cost of "IVF treatment" over "no IVF treatment" was $1 391.91 from the patient's perspective, $2 545.95 from the insurer/payer's perspective, and $3 937.86 from society's perspective.

The researchers warn that the results expressed on a per-patient basis are misleading because the experimental group was observed for a longer period than the control group. They also suggest that the requirements of a longer duration of infertility or particular types of infertility (eg. blocked tubes) for admission into an IVF program, or a longer waiting period with alternative treatment, might be more cost-effective than the current practice of immediate IVF treatment for all infertility indications. They also point out that the unanticipated scheduling delays, which resulted in the experimental group undergoing fewer IVF cycles, may have contributed to a bias against it.

The researchers emphasize that theirs was a study of a specific program, and different results might be produced by an evaluation with more control over the delay before the first IVF cycle, or one with more IVF cycles per experimental-group patient. Therefore, they stress, this is a study of the effectiveness, and not efficacy, of a specific IVF program.

Introduction

In vitro fertilization (IVF) is a relatively new technique for treating infertility. The first case reports of pregnancy following extra-corporeal fertilization involved women with severe tubal disease. Since the appearance of these reports, the justification and apparent indications for IVF treatment have been extended to other causes of infertility, including endometriosis, seminal deficiencies, and idiopathic causes. Although IVF has proven to be modestly efficacious for treating completely obstructed fallopian tubes of some patients, these specific results cannot be assumed to extend to other forms of infertility. More important, the effectiveness and cost-effectiveness of IVF treatment for many causes of infertility has not, to date, been demonstrated.

The evidence that would enable researchers to fully evaluate this technology is incomplete and often controversial. Positive case reports of births in the literature and the popular media have led to the belief by the general public that the procedure has a high success rate. However, the research designs of Canadian and international studies focus on the success (or failure) rates of patients undergoing IVF treatment only, without taking into account what would occur without the intervention. Furthermore, they do not evaluate the technology within a formal, comparative, economic framework (i.e., comparing the *extra* costs of "IVF treatment" with "no IVF treatment" relative to the *extra* clinical effects it produces).

Objectives

In light of these gaps in the literature, we attempted to evaluate the effectiveness and cost- effectiveness of "IVF treatment" versus "no IVF treatment" in terms of viable pregnancies, parturitions, and live births. More specifically, the objectives of the study were to (1) conduct a cost analysis[1] of "IVF treatment" versus "no IVF treatment," and (2) determine the cost-effectiveness of "IVF treatment" versus "no IVF treatment," or if appropriate, the least costly alternative treatment. The third objective was to estimate the costs of selected other infertility treatments and of hospitalizations related to pregnancy.

Methods

Clinic Setting and Protocol

Chedoke-McMaster's fertility clinic is located in Hamilton, Ontario and is one of nine clinics that provide IVF treatment in Ontario. Its catchment

area is all of Ontario, but the majority of its patients are from the Hamilton-Wentworth and Niagara regions. The clinic has a treatment volume of 13 000 visits annually, of which approximately one-third are IVF-related. At the time of this study, the IVF program had an admission criterion of at least one year of infertility (the mean was four years) and did not treat women over 40 years of age. In general, a maximum of four completed IVF cycles was allowed per couple. After two unsuccessful IVF attempts, additional sperm and ovum testing was necessary and donor sperm might then be used.

Study Design

The study was a randomized controlled trial that compared infertile couples undergoing IVF treatment with those awaiting treatment. Over the study period, which was between February 1987 and April 1990, 205 couples were randomly assigned to the experimental group (early treatment) and 194 couples were randomly assigned to the control group (delayed treatment). Patient recruitment into the study began in February 1987 and ended in April 1989. It started with general information sessions about IVF treatment, where couples were informed that admission into the program required their participation in a study in which they would be randomly allocated to treatment in the first available six-month period (experimental group) or the following six-month period (control group). Couples randomized to the control group would eventually receive treatment, but only after the waiting period. Randomization was stratified according to the following diagnostic categories of infertility: seminal defects, tubal disease, endometriosis, and idiopathic causes. (The design of the trial is presented in Appendix 1).

Sample sizes for the study were calculated assuming a spontaneous pregnancy rate in the control group of 15%. The sample size required to detect an increase in the absolute rate to 25% in the experimental group, with an alpha of 0.05 and a beta of 0.90, was 197 per group. The hypothesized 10 percent absolute difference was considered to be clinically significant.

Collection and Analysis of the Clinical Data

Outcome measures collected for the study included viable pregnancies, parturitions (deliveries), single births, multiple births, spontaneous abortions, ectopic pregnancies, and stillbirths. Other variables that affect the calculation of effectiveness (i.e., incomplete cycles, pre-treatment pregnancies in the experimental group, and drop-outs) and other demographic variables (i.e., duration of infertility, age at referral) were also collected.

Although couples were randomized to either early (experimental) or delayed (control) treatment, it was uncertain at the outset of the study whether there would be a difference in the drop-out rates of the two groups.

In addition, because of the study design, it was certain that the observation period for the experimental group would be longer than that for the control group. Both these factors could impact differentially on the length of the follow-up for the two groups. Therefore, we decided to collect information on the length of the follow-up period and the time to outcomes, in addition to straight proportional pregnancy, parturition, and live birth rates.

The primary outcome measure was pregnancy rates and the secondary outcome measures were parturition and live birth rates. The rates of the experimental and control groups were initially compared and analyzed using the Mantel-Haenzel chi-square test for comparisons of proportions. If there was a statistically significant difference in the lengths of follow-up for the two groups, then survival analysis would form the basis of the analysis.

Cost Analysis of "IVF Treatment" and "No IVF Treatment"

A cost analysis can be conducted from a number of different perspectives. Costs that are relevant from one perspective may not be relevant from another. For example, in Ontario the patient pays for medications needed for IVF, while the Ministry of Health pays for the physician and clinic costs. Therefore, it is important to identify from which perspective(s) the cost analysis is being undertaken for the data collection and valuation phase of the study, and to specify this in reporting the results. We conducted cost analyses from three different perspectives: the patient (or family), the insurer/payer (the Ministry of Health), and society. All data collection forms were constructed to allow the cost analysis to be conducted from these three perspectives.

The cost analysis was designed to collect information on the control and experimental groups. Although the direct treatment costs of IVF are the most obvious costs for the experimental group, they are not the only relevant ones. Most infertility treatment involves not only clinic and other hospital department costs, but also direct costs to patients, and indirect costs (productivity loss, i.e., time off work). In addition, there may be expenses for the patients in the waiting (control) group if they are receiving other infertility treatments while they are waiting for IVF treatment. For both the control and experimental groups, we collected and analyzed the cost data according to the following categories:

1. Direct medical costs:
   - (a) IVF clinic;
   - (b) Alternative treatment;
   - (c) Other hospital departments; and
   - (d) Physicians.

2. Direct patient costs:
   (a) Drugs;
   (b) Transportation; and
   (c) Parking.
3. Induced medical costs (treatment of complications and side-effects):
   (a) Hospital;
   (b) Physicians; and
   (c) Other.
4. Indirect costs (productivity losses).

These categories are commonly used in economic evaluations. The distinctions between them are somewhat arbitrary; they are used primarily to facilitate organization of the analysis and reporting of the results.

Data for each cost category is collected according to the perspective from which it is taken (i.e., the patient, the insurer/payer, or society). An expense is included or not under one or more of the above cost categories depending upon whose perspective is used. Table 1 displays the relationships between cost categories and cost perspectives.

Table 1. Relationships Between Cost Perspectives and Cost Categories

	Cost perspective		
Cost category	**Patient**	**Insurer/payer**	**Society**
Direct — medical			
Clinic	no	yes	yes
Alternative treatment	no	yes	yes
Other hospital departments	no	yes	yes
Physicians	no	yes	yes
Direct — patient			
Drugs	yes	no	yes
Transportation	yes	no	yes
Parking	yes	no	yes
Other	yes	no	yes
Induced — medical (experimental group only)			
Hospital	no	yes	yes
Physicians	no	yes	yes
Other	no	yes	yes
Indirect	yes	no	yes

As can be seen from Table 1, the perspective of society is the most comprehensive and encompasses the other two perspectives (i.e., that of the patient and insurer/payer). This is the perspective that is most widely advocated for economic evaluations. The methods used to collect data for each of these categories are discussed in detail below.

Direct Medical Costs

Clinic costs include: personnel (nurses, technicians, and social workers); supplies (medical, surgical, and office); capital equipment (medical and non-medical); and hospital overhead (utilities and services from other departments). Alternative treatment costs are costs reported by patients for alternative infertility treatment undertaken while participating in the program. For the control group, a survey of the charts of 100 randomly selected couples on a separate IVF waiting list was used to estimate the types and costs of alternative treatment.

Other hospital department costs include the costs of services from the IVF laboratory and from the hematology, clinical chemistry, microbiology, pathology, and radiology departments; and the hospital overhead for each of these departments. Physician costs include: OHIP professional billing for treatment; interpretation of diagnostic tests; and consultations.

In order to allocate a share of hospital overhead to the clinic and other hospital departments, a costing model was developed for Chedoke-McMaster Hospitals. As recommended for hospital allocation procedures, we used a simultaneous, fully allocated costing technique.

Direct Patient Costs

These are out-of-pocket costs incurred by patients and their families as a result of treatment (e.g., drugs, transportation, and parking). Direct patient costs were calculated based on a sample of patients from both the experimental and control groups. Forty randomly selected experimental-group couples were asked to complete a Patient Expense Record designed specifically for expenses related to infertility treatment. Direct patient costs for couples in the control group were based on the type of treatment they received while on the waiting list. A survey of the charts of 100 randomly selected couples on a separate IVF waiting list was used to determine the type of treatment received while awaiting IVF treatment. Costs were then estimated using average treatment protocols and the costing model developed for the hospital.

Induced Medical Costs (Experimental Group Only)

These are the costs of medical care that result from complications and side-effects of the treatment. Sequelae of treatment include: spontaneous abortions; ectopic pregnancies; excessive bleeding following treatment; and other negative reactions to treatment or drugs. Costs of medical care related to ectopic pregnancies and spontaneous abortions were abstracted from medical records using a Medical Records Abstraction Form designed specifically for the study. For other sequelae of treatment, the same 40

experimental-group couples were asked to document all hospitalization, visits to the doctor, and drug expenses that resulted from complications or side-effects of the treatment. This information was recorded in the Patient Expense Record, and where hospitalizations were reported, the research nurse abstracted the data from hospital records.

Indirect Costs

These consist of productivity losses (i.e., time off work) as a result of treatment or the negative sequelae of treatment. The forty experimental-group couples were also asked to record all time taken off work as a result of treatment or the negative sequelae of treatment. For control-group couples, estimates of productivity lost as a result of alternative treatment received while on the waiting list were based on time off work reported by experimental-group couples for similar treatment. Average male and female wage rates for Ontario were used to calculate productivity losses.

IVF Completion Points

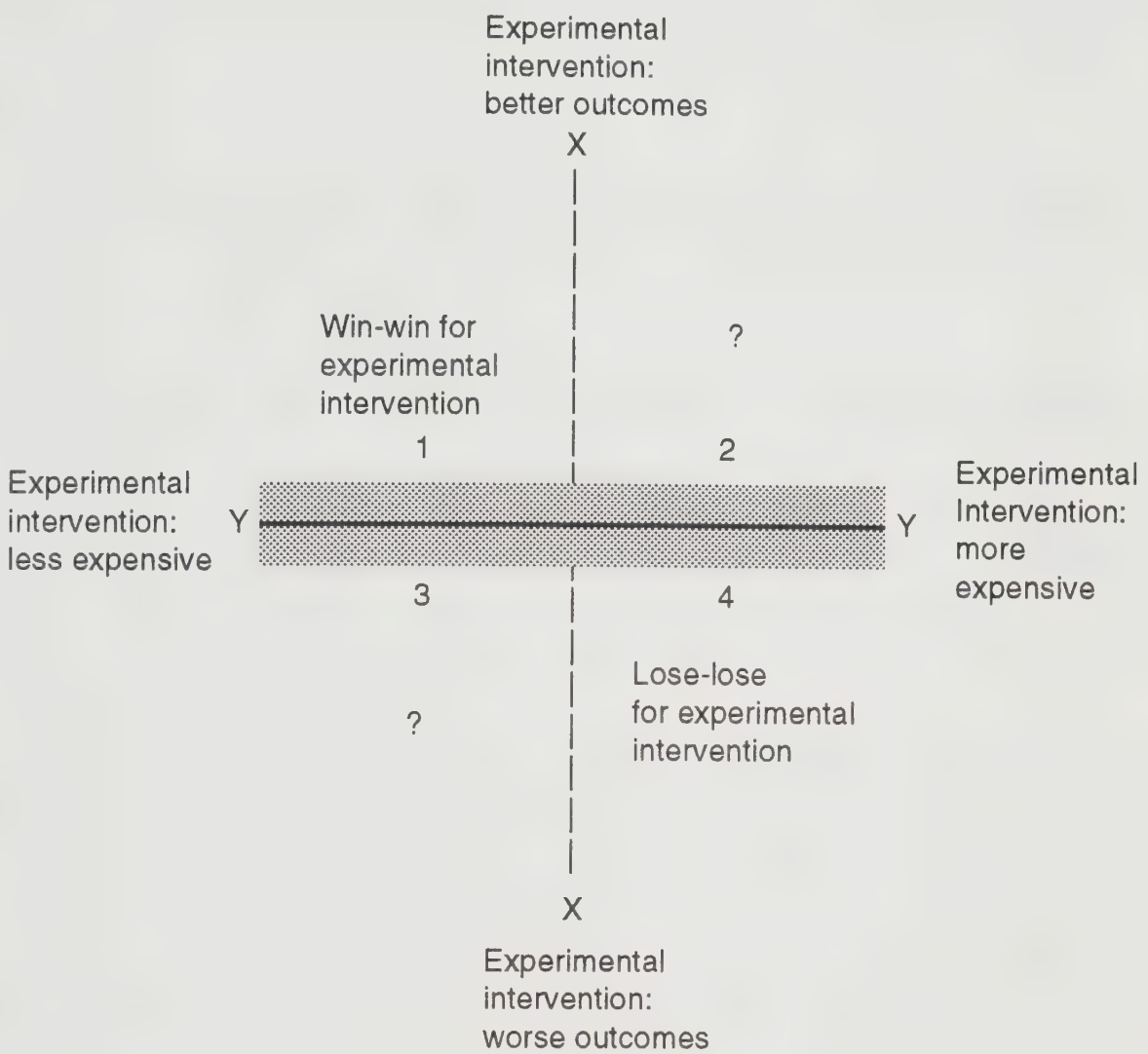
IVF treatment is not an all or none proposition. Once it has been initiated, there are a number of stages during which it can be discontinued. Therefore, direct medical costs, direct patient costs, and indirect costs related to IVF treatment depend on whether the treatment was completed or whether it was cancelled. To increase the accuracy of the cost estimates, we identified three major "completion points" of treatment: (a) the procedure was cancelled during ovulation induction or before egg retrieval; (b) the procedure was cancelled during retrieval or before the embryo transfer; and (c) the procedure was completed or the embryo transferred. For costing purposes, each patient's actual stage of completion for each IVF treatment cycle initiated was matched against the cost for each completion point.

Cost-Effectiveness and Cost-Minimization Analysis[2]

With this study, as with most studies, the results can be analyzed in a number of ways using a number of assumptions. With a cost-effectiveness analysis, it is particularly important to explore the alternatives. It would be inappropriate, for example, to conduct a cost-effectiveness analysis or calculate cost-effectiveness ratios if there were no statistically significant differences in the outcomes. Under these circumstances, the appropriate analysis would be a cost-minimization analysis. Figure 1 is useful as an aid to determining when to use cost-effectiveness analysis and when to use cost-minimization analysis.

In quadrants 1 and 4, a cost-effectiveness analysis is not necessary because one of the interventions is a clear winner in both costs and outcomes (i.e., a dominant strategy). Where there are no statistically significant differences between the outcomes of the two interventions (in the shaded areas slightly above and slightly below YY), the analysis is reduced to a cost-minimization analysis. Only if the outcomes fall into the remaining sections of quadrants 2 and 3 should a cost-effectiveness

Figure 1. Possible Combinations of Costs and Outcomes in Comparisons of Two Interventions



analysis be conducted, because only then is there a clear trade-off between higher costs and better outcomes for one intervention over the other.

Figure 1 also helps demonstrate a problem that may arise when alternative assumptions or types of analysis are used. If the costs or outcomes of the two interventions are similar, it is possible that an alternative assumption or type of analysis may shift the evaluation into a different quadrant. If this does not occur, the robustness of the results will likely increase. If it does occur, however, it is particularly important to remain with the baseline analysis originally specified as the main analysis and consider the alternative assumptions only for discussion purposes.

In comparing the pregnancy, parturition, and live birth outcomes of the control and experimental groups, straight proportions and survival analysis were both used. In addition, because various interested parties may have conflicting opinions about which variables to include when calculating success rates, the impact of including and excluding some of these variables was examined. The relationships between the variables that affect the calculation of success rates and the groups whose interests they may represent appear in Table 2.

Table 2. Relationships Between Interest Groups and Choice of Input Variables to Include in the Calculation of Outcomes

	Input variable	
Interest group	**Pre-treatment pregnancies**	**Drop-outs**
Patient	yes	no
Insurer/payer	no	no
Society (research methodologist)	yes	yes

It could be argued that since patients are mainly concerned with the outcome of being pregnant — regardless of how the pregnancy came about — from their perspective, pre-treatment pregnancies should be included in the calculation of success rates. The patient may believe that drop-outs should not be included because dropping out is the patient's decision, and including drop-outs would not reflect their true chances of becoming pregnant if "they stuck it out." From the insurer/payer's perspective (i.e., the Ministry of Health), it could be argued that pre-treatment pregnancies and drop-outs should not be included because the patients concerned are not being treated. And finally, it could be argued on pure intention-to-treat grounds (the perspective of society, or the research methodologist) that both pre-treatment pregnancies and drop-outs should be included.

The three outcome measures (i.e., clinical pregnancy, parturition, and live birth); the three cost perspectives (i.e., the patient, the insurer/payer, and society); and the three interest groups (i.e., the insurer/payer, the patient, and society), produce 27 possible combinations of evaluations. Only the combinations down the diagonal in Table 3 are relevant from the perspectives of the respective interest groups, so we only analyzed these combinations for the three outcome measures.

Table 3. Relationships Between Cost Perspectives and Interest Groups

	Cost perspective		
Interest group	**Patient**	**Insurer/payer**	**Society**
Patient	XXX		
Insurer/payer		XXX	
Society (research methodologist)			XXX

Costs of Selected Other Infertility Treatments

Although not part of the formal comparative evaluation, the costs of selected other infertility treatments were also estimated. The calculations were based on patients' charts, clinic protocols, and information from experts in the clinic. Treatment protocols are not homogeneous and are very patient-specific; nevertheless, we attempted to derive typical protocols for each type of infertility treatment. It should be emphasized that more accurate protocols can only come from formal evaluations with detailed patient follow-up.

Because a substantial portion of total treatment costs arise from the initial screening and diagnostic tests, the costs of the first and second treatments or cycles were estimated for each type of treatment. Costs associated with the initial screening and diagnostic work-up are included in the cost estimate for the first treatment or cycle. These estimates approximate the cost for couples when they first enter the clinic. Cost estimates for the second treatment or cycle reflect subsequent or ongoing treatment costs.

Costs were calculated for the following infertility treatments:

1. diagnostic screening and waiting period;
2. ovulation induction medications (Clomid®);
3. ovulation induction medications (Pergonal®);
4. therapeutic donor insemination (TDI);
5. intrauterine insemination (IUI);
6. IVF;
7. tuboplasty; and
8. any treatment for endometriosis (Lupron®).

These costs were analyzed from the perspective of society, and information on direct medical, direct patient, and indirect costs (productivity losses) was collected. Direct patient expenses and productivity losses were estimated based on assumptions regarding the number of visits and length of time spent in hospital out-patient departments and in-patient wards.

Costs of Selected Hospitalizations Related to Pregnancy

Costs for the following types of hospitalizations were estimated:

1. normal delivery (vaginal and term);
2. caesarian section;
3. ectopic pregnancy; and
4. spontaneous abortion, miscarriage, and D&C.

These calculations were based on a review of patient charts and produced in consultation with experts working in the fertility clinic. Direct medical costs and indirect costs were included.

Results

Demographics

There were 205 couples assigned to the experimental group (early treatment) and 194 couples assigned to the control group (delayed treatment). There was no difference between the groups in terms of age at referral to the clinic (experimental — 32.3 +/- 3.8; control — 32.5 +/- 3.8), duration of infertility at referral (experimental — 5.9 +/- 3.2; control — 5.5 +/- 3.2 years), or stratified category of primary clinical diagnosis.

Length of Patient Follow-up Period

The first step in the data analysis was to determine whether there was a difference between the lengths of the two groups' follow-up periods. A longer follow-up means that one group is at risk of becoming pregnant — through treatment-assisted and/or natural conception — for longer than the other. A longer follow-up period could impact on overall success rates; if there are differences, survival analysis would be the appropriate analysis. Factors that could have a major influence on the length of the follow-up period include differential drop-out rates between the two groups and the longer potential observation period for the experimental group.

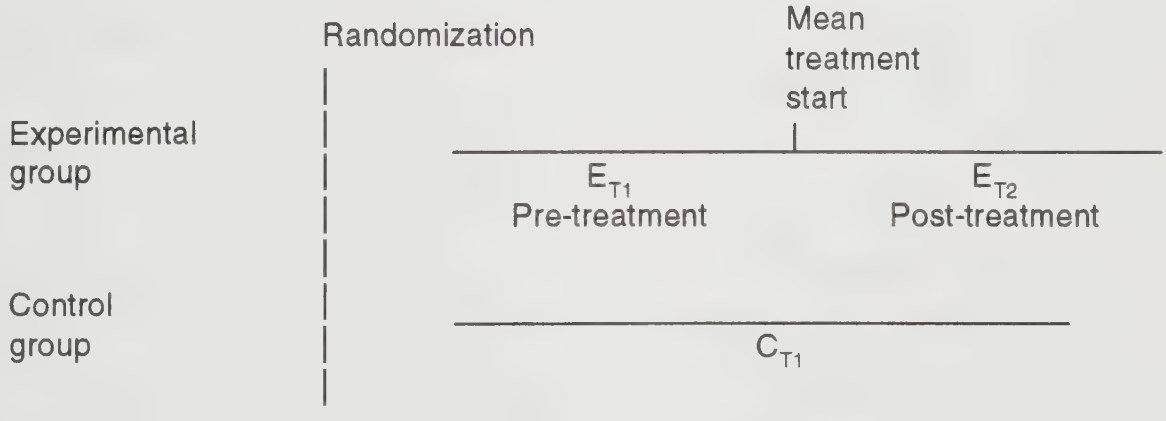
Of the 205 experimental-group couples, 45 (22%) dropped out of the program before receiving treatment, and of the 194 control-group couples, 61 (31%) dropped out during the waiting period. These differential drop-out rates were significant ($p = .03$), and this factor, together with the longer

observation period for the experimental group, resulted in a significantly longer total follow-up period for the experimental group (14.68 months versus 8.74 months, $p < .001$). Although this allowed us to observe a greater number of treatment cycles on the experimental group (286 cycles initiated), it also meant they were at risk of becoming pregnant almost six months longer than the control group. Because of this differential follow-up period, we used survival analysis rather than straight proportional analysis to compare differences in the two groups' pregnancy, parturition, and live birth rates.

Time to Treatment

A second challenge to the study design arose as a result of delays in scheduling appointments in the clinic. Instead of receiving treatment within the first few months of randomization, the experimental group experienced a mean time to treatment of 8.1 months. This meant that the experimental group was not receiving IVF treatment for almost half of its total observation period, on average. The intention of the trial was to compare the post-treatment period (E_{T2}) with the control period (C_{T1}) (Figure 2), not the pre- and post-treatment periods ($E_{T1} + E_{T2}$) with the control period (C_{T1}).

Figure 2. Experimental and Control Groups' Observation Periods



Scheduling delays and differential lengths of observation notwithstanding, the comparison between the pre- and post-treatment periods and the control period was the pure intention-to-treat analysis and therefore formed the baseline analysis for the study. Since the original hope of the study was to compare the post-treatment period with the control period, and since the scheduling delays in the clinic were beyond our control, we decided to include this comparison in the main analysis. For completeness, we also compared the pre-treatment and control observation periods.

Clinical Results

In the experimental group of 205 couples, 139 patients had at least one cycle initiated (or reached the post-treatment observation period). There were 20 IVF-assisted pregnancies that resulted in 13 parturitions and 17 live births. There were also 13 pregnancies in the pre-treatment observation period that resulted in 9 parturitions and live births. Among the 194 control-group couples, there were 13 spontaneous pregnancies and 8 parturitions and live births. The main findings of the study are summarized in Tables 4 to 6. In Table 4 we show the outcomes of the pre- and post-treatment observation periods and those of the control period (C_{T1}) for the three interest groups (i.e., the patient, the insurer/payer, and society, or the research methodologist). In Table 5 we show the outcomes of the pre-treatment observation period and those of the control period, and in Table 6 we show the outcomes of the post-treatment observation period and those of the control period. Since pre-treatment pregnancies may be relevant from the patient's perspective, results are reported from the points of view of the patient and society in Table 5. By definition, pre-treatment pregnancies and drop-outs are excluded from the post-treatment observation period, so the results in Table 6 are from only the perspective of society, or the research methodologist.

The pregnancy, parturition, and live birth rates in Tables 4 to 6 are presented on a per-patient basis and on a per-month-at-risk basis. Although results expressed on a per-patient basis indicate the proportion of patients who became pregnant, or how many babies were born during the study, they can be misleading if follow-up periods for the two groups are different. For example, comparing pregnancy rates on a per-patient basis may give the impression that one intervention has a better success rate, when in fact it is because the group had a longer observation period. Time (months at risk) is also an important dimension when discussing pregnancy rates, and it should be incorporated in the analysis. Although survival techniques were used for the baseline analysis, a crude contingency analysis (Mantel-Haenszel) conducted on a per-month-at-risk basis suggests there were no significant differences between the two groups in terms of pregnancies, parturitions, and live births. Thus, when the longer observation period is taken into account, no differences in live births were observed.

Table 7 presents the cumulative pregnancy rates of IVF treatment. Included are the pregnancy rates of all cycles initiated (completed and cancelled) and the pregnancy rates of only the cycles that were completed. These are the rates that are commonly cited. It should be noted that although the cumulative pregnancy rate after three or more completed IVF cycles appears to be around 10 percent, the actual "take-home baby" rate is influenced by other factors such as drop-outs and incomplete or cancelled cycles (see Appendix 2). These rates alone do not indicate the incremental (or additional) benefit of "IVF treatment" over and above

conventional or "no IVF treatment"; this is addressed in Tables 4 to 6 and in the following section.

Table 4. Pregnancy, Parturition, and Live Birth Rates for the Pre- and Post-Treatment Observation Periods Versus the Control Period — By Interest Group

	Experimental ($E_{T1} + E_{T2}$)		Control (C_{T1})		
Interest group	Per patient	Per month at risk	Per patient	Per month at risk	p-value*
	Viable pregnancies				
Patient	33/160 (20.6%)	33/2 835 (1.2%)	13/133 (9.8%)	13/1 436 (0.9%)	p = .439
Insurer/payer	20/147 (13.6%)	20/2 776 (0.7%)	13/133 (9.8%)	13/1 436 (0.9%)	p = .519
Society	33/205 (16.1%)	33/3 010 (1.1%)	13/194 (6.7%)	13/1 695 (0.8%)	p = .270
	Parturitions				
Patient	22/160 (13.8%)	22/3 067 (0.7%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .410
Insurer/payer	13/147 (8.8%)	13/2 901 (0.4%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .767
Society	22/205 (10.7%)	22/3 243 (0.7%)	8/194 (4.1%)	8/1 822 (0.4%)	p = .287
	Live births				
Patient	26/160 (16.3%)	26/3 067 (0.8%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .206
Insurer/payer	17/147 (11.6%)	17/2 901 (0.6%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .751
Society	26/205 (12.7%)	26/3 243 (0.8%)	8/194 (4.1%)	8/1 822 (0.4%)	p = .129

* Calculated on months at risk.

Notes: E_{T1}, pre-treatment observation period, E_{T2}, post-treatment observation period, C_{T1}, control observation period.

Table 5. Pregnancy, Parturition, and Live Birth Rates for the Pre-Treatment Observation Period Versus the Control Period — By Interest Group

Interest group	Experimental (E_{T1}) Per patient	Experimental (E_{T1}) Per month at risk	Control (C_{T1}) Per patient	Control (C_{T1}) Per month at risk	p-value*
	Viable pregnancies				
Patient	13/160 (8.1%)	13/1 261 (1.0%)	13/133 (9.8%)	13/1 436 (0.9%)	p = .739
Society	13/205 (6.3%)	13/1 599 (0.8%)	13/194 (6.7%)	13/1 695 (0.8%)	p = .881
	Parturitions				
Patient	9/160 (5.6%)	9/1 332 (0.7%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .564
Society	9/205 (4.3%)	9/1 708 (0.5%)	8/194 (4.1%)	8/1 822 (0.4%)	p = .706
	Live births				
Patient	9/160 (5.6%)	9/1 332 (0.7%)	8/133 (6.0%)	8/1 563 (0.5%)	p = .564
Society	9/205 (4.3%)	9/1 708 (0.5%)	8/194 (4.1%)	8/1 822 (0.4%)	p = .706

* Calculated on months at risk.

Table 6. Pregnancy, Parturition, and Live Birth Rates for the Post-Treatment Observation Period Versus the Control Period — By Interest Group

Interest group	Experimental (E_{T2}) Per patient	Experimental (E_{T2}) Per month at risk	Control (C_{T1}) Per patient	Control (C_{T1}) Per month at risk	p-value*
	Viable pregnancies				
Society	20/139 (14.4%)	20/1 406 (1.4%)	13/177 (7.3%)	13/1 695 (0.8%)	p = .076

Table 6. (*cont'd*)

	Parturitions				
Society	13/139 (9.4%)	13/1 528 (0.9%)	8/177 (4.5%)	8/1 822 (0.4%)	p = .132
	Live births				
Society	17/139 (12.2%)	17/1 528 (1.1%)	8/177 (4.5%)	8/1 822 (0.4%)	p = .024

* Calculated on months at risk.

Table 7. Cumulative Pregnancy Rates for Experimental Group — By Cycle

Cycle	At Risk (n)	Pregnancies (n)	Cumulative Pregnancy Rate (%)
	All cycles initiated		
1	139	8	5.8
2	85	6	6.3
3	42	5	7.1
4	12	1	7.2
5	7	0	7.0
6	1	0	7.0
	Completed cycles only		
1	99	8	8.1
2	54	6	9.2
3	31	5	10.3
4	7	1	10.5
5	6	0	10.2
6	1	0	10.1

Survival Analysis

Survival analysis is a technique whereby the success (or failure) of one treatment or alternative is compared with the success (or failure) of one or more other treatments or alternatives. The area under one survival curve is compared with the area under another survival curve to test for statistically significant differences. The endpoint in survival analysis is not necessarily death. "Survival" can also be defined as responses to, or

outcomes from, a given treatment. Patients are usually removed from a survival analysis when they are lost to follow-up, at the end of the total trial or observation period, or when the outcome of interest occurs. The strength of survival analysis lies in the fact that the denominator in the survival analysis is continuously adjusted to reflect the number of patients (or cases) at risk at any time. With a straight proportional analysis, the denominator is assumed constant throughout the observation period, thus the former analysis is more accurate in studies where the length of patient follow-up is variable.

For this study, survival was defined as the proportion of patients not pregnant at any time. The results of the survival analysis on pregnancies are presented in Table 8. Included are the results of comparisons of all three observation periods (i.e., pre- and post-treatment with control, pre-treatment with control, and post-treatment with control), by interest group. Cumulative survival is defined as the proportion of patients not pregnant at the end of the observation period. There were no significant differences between the pregnancy rates of the experimental and control groups for either observation period. The pregnancy rates of the experimental group for the pre-treatment period and of the control group for the entire follow-up period were almost identical (i.e., E_{T1} versus C_{T1}, p = .9735). This is not surprising, given the randomized design of the study and the fact that the patients had similar ages, durations of infertility, and primary clinical diagnoses at entry into the study.

Table 8. Cumulative Survival of Pregnancies — Observation Period and Interest Groups

	Cumulative survival		
Interest group	**Experimental**	**Control**	**p-value**
	Pre- and post-treatment (E_{T1} + E_{T2}) versus control (C_{T1}) observation periods		
Patient	.64	.71	p = .7479
Insurer/payer	.70	.71	p = .0377
Society	.64	.72	p = .6240
	Pre-treatment (E_{T1}) versus control (C_{T1}) observation periods		
Patient		n.a.	
Insurer/payer			
Society	.77	.72	p = .9735
	Post-treatment (E_{T2}) versus control (C_{T1}) observation periods		
Patient		n.a.	
Insurer/payer			
Society	.67	.72	p = .2444

Cost Analysis of "IVF Treatment" and "No IVF Treatment"

IVF treatment costs were estimated on the basis of each patient's completion point for each IVF cycle initiated. The number of IVF cycles initiated, by completion point, is presented in Table 9. Each patient's actual stage of completion for each IVF treatment cycle initiated was matched against the cost for each of the three completion points.

Table 9. Number of IVF Cycles Initiated — By Completion Point

Completion point of cycle	(n)
Cancelled during induction/prior to retrieval	45
Cancelled during retrieval/prior to embryo transfer	43
Completed to end/embryo transferred	198
Total cycles initiated	286

The infertility treatment undertaken by 100 randomly selected couples while on the waiting list for IVF is presented in Table 10. It was assumed that the control-group couples would receive only one cycle or treatment of each type while on the waiting list. Although couples on the IVF waiting list could receive more than one cycle or treatment while waiting for IVF treatment, it was unlikely that they would receive many cycles or treatments during the short observation period for the control couples.

Table 10. Non-IVF Infertility Treatment Undertaken by Patients While on IVF Waiting List

	(%)
No treatment	34
Clomid® induction	31
Intrauterine insemination and Clomid® induction	6
Intrauterine insemination and Pergonal® induction	3
Intrauterine insemination	6
Therapeutic donor insemination	3
Tuboplasty	14
Lupron® therapy	3

Since costs depend on the observation periods chosen, two periods were identified for the cost analysis: pre- and post-treatment ($E_{T1} + E_{T2}$) versus the control period (C_{T1}), and post-treatment (E_{T2}) versus the control period (C_{T1}). Table 11 presents the average costs per experimental-group patient for the pre- and post-treatment, and post-treatment observation periods. The higher costs for the post-treatment observation period reflect the fact that the bulk of the total experimental-group costs are actually incurred by a smaller number of patients (n = 139). In the pre- and post-treatment observation periods, the costs for the smaller group of patients are spread over all patients (n = 205), a number of whom incurred few or no costs. All costs are expressed in 1990 Canadian dollars.

Table 11. Average Costs Per Experimental-Group Patient — By Observation Period, Cost Perspective, and Cost Category in 1990

Cost category	Cost perspective		
	Family ($)	Insurer/payer ($)	Society ($)
	Pre- and post-treatment ($E_{T1} + E_{T2}$) observation period		
Direct — medical	n.a.	3 827.44	3 827.44
Direct — patient	1 214.37	n.a.	1 214.37
Induced — medical	n.a.	63.91	63.91
Indirect	360.68	n.a.	360.68
Total	1 575.05	3 891.35	5 466.40
	Post-treatment (E_{T2}) observation period		
Direct — medical	n.a.	5 138.80	5 138.80
Direct — patient	1 781.09	n.a.	1 781.09
Induced — medical	n.a.	54.89	54.89
Indirect	503.96	n.a.	503.96
Total	2 285.05	5 193.69	7 478.74

n.a. - not available

Table 12 presents the average costs per control-group patient. They reflect the standard costs of the diagnostic work-up (73 percent of total

costs) and of alternative treatment received. The standard costs of the diagnostic work-up are common to both groups and are cancelled out when incremental costs are calculated.

Table 12. Average Costs per Control-Group Patient for the Control Observation Period (C_{T1})

	Cost perspective		
Cost category	Family ($)	Insurer/payer ($)	Society ($)
Direct — medical	n.a.	1 345.40	1 345.40
Direct — patient	81.88	n.a.	81.88
Indirect	101.26	n.a.	101.26
Total	183.14	1 345.40	1 528.64

Cost-Effectiveness and Cost-Minimization Analyses

The survival and cost analyses indicate that the comparison of "IVF treatment" with "no IVF treatment" is on, or very close to, the horizontal line YY in Figure 1. IVF treatment is more expensive and there are no statistically significant differences in the pregnancy, parturition, or live birth rates compared with those of couples on the waiting list. Therefore, the analysis is reduced to a cost-minimization analysis. Because the analysis did not demonstrate statistically significant differences in any of the main outcome measures (i.e., pregnancies, parturitions, and live births), it is not necessary to report the cost-minimization results for each of the three outcome measures separately; the results for the three outcome measures are identical.

The average incremental cost per patient of "IVF treatment" versus "no IVF treatment" is presented in Table 13. In the comparison of the pre- and post-treatment periods ($E_{T1} + E_{T2}$) with the control period (C_{T1}), the cost was $1 391.91 from the patient's perspective, $2 545.95 from the insurer/payer's perspective (the Ministry of Health), and $3 937.86 from society's perspective. In the comparison of the post-treatment period with the control period, the cost was $2 101.91 from the patient's perspective, $3 848.29 from the insurer/payer's perspective, and $5 950.20 from society's perspective. The higher incremental costs per patient in the last comparison reflect the fact that the bulk of the total experimental-group costs are actually incurred by a smaller number of patients (n = 139). In the pre- and post-treatment versus control period comparison, the costs for

the smaller group of patients are spread over all patients (n = 205), a number of whom incurred few or no costs.

Table 13. Average Incremental Cost Per Patient of "IVF Treatment" Versus "No IVF Treatment" — By Cost Perspective, Cost Category, and Observation Period in 1990

Cost category	Cost perspective		
	Family ($)	Insurer/payer ($)	Society ($)
	Pre- and post-treatment ($E_{T1} + E_{T2}$) versus control (C_{T1}) observation periods		
Direct — medical	n.a.	2 482.04	2 482.04
Direct — patient	1 132.49	n.a.	1 132.49
Induced — medical	n.a.	63.91	63.91
Indirect	259.42	n.a.	259.42
Total	1 391.91	2 545.95	3 937.86
	Post-treatment (E_{T2}) versus control (C_{T1}) observation periods		
Direct — medical	n.a.	3 793.40	3 793.40
Direct — patient	1 699.21	n.a.	1 699.21
Induced — medical	n.a.	54.89	54.89
Indirect	402.70	n.a.	402.70
Total	2 101.91	3 848.29	5 950.20

Costs of Selected Other Forms of Infertility Treatments

Cost estimates for selected other infertility treatments, by cost category, are presented in Tables 14 to 21 (in 1990 Canadian dollars). Although it is not strictly a type of treatment, diagnostic screening and then waiting to "see what happens" is common among couples when they first seek treatment for infertility (Table 14). Costs associated with IVF treatment are broken down by the three completion points (Table 19).

All cost estimates are from the perspective of society. We did not attempt to estimate the extent or the cost of treating complications or side-effects of treatment (induced medical costs). For each type of infertility treatment, cost estimates are provided for the first and second treatments

or cycles. Costs associated with the initial screening and diagnostic work-up are included in the cost estimate for the first treatment or cycle. These estimates approximate the cost for couples when they first enter the clinic. The cost estimates for the second treatment or cycle are a reflection of later or ongoing treatment costs. More detailed costs for initial or subsequent treatments can only be obtained through a more detailed patient follow-up.

Table 14. Cost of Diagnostic Screening and Waiting Period — By Cost Category in 1990

Cost category	Cost ($)
Direct — medical	1 065.64
Direct — patient	20.80
Indirect	39.48
Total	1 125.92

Table 15. Cost of Clomid® Induction Treatment — By Cost Category in 1990

Cost category	First cycle ($)	Second cycle ($)
Direct — medical	1 170.52	104.88
Direct — patient	63.40	42.60
Indirect	78.96	39.48
Total	1 312.88	186.96

Table 16. Cost of Pergonal® Induction Treatment — By Cost Category in 1990

Cost category	First cycle ($)	Second cycle ($)
Direct — medical	2 074.18	1 008.54
Direct — patient	876.64	855.84
Indirect	197.40	157.92
Total	3 148.22	2 022.30

Table 17. Cost of Therapeutic Donor Insemination Treatment — By Cost Category in 1990

Cost category	First cycle ($)	Second cycle ($)
Direct — medical	1 703.88	356.11
Direct — patient	284.62	263.82
Indirect	98.70	59.22
Total	2 087.20	679.15

Table 18. Cost of Intrauterine Insemination Treatment — By Cost Category in 1990

Cost category	First cycle ($)	Second cycle ($)
Direct — medical	1 467.18	401.54
Direct — patient	230.04	209.24
Indirect	118.44	78.96
Total	1 815.66	689.74

Table 19. Cost of IVF Treatment — By Completion Point and Cost Category in 1990

Cost category	First cycle ($)	Second cycle ($)
	Cancelled during induction/prior to retrieval	
Direct — medical	1 823.16	757.52
Direct — patient	828.30	807.50
Indirect	142.13	102.65
Total	2 793.59	1 667.67

Table 19. (*cont'd*)

	Cancelled during retrieval/prior to embryo transfer	
Direct — medical	2 909.38	1 843.74
Direct — patient	868.70	847.90
Indirect	171.08	131.60
Total	3 949.16	2 823.24
	Completed to end/embryo transferred	
Direct — medical	3 352.51	2 286.87
Direct — patient	888.90	868.10
Indirect	302.68	263.20
Total	4 544.09	3 418.17

Table 20. Cost of Tuboplasty Treatment by Cost Category in 1990

Cost category	First treatment ($)	Second treatment ($)
Direct — medical	3 283.25	2 217.61
Direct — patient	69.55	48.75
Indirect	513.24	473.76
Total	3 866.04	2 740.12

Table 21. Cost of Lupron® Treatment by Cost Category in 1990

Cost category	First treatment ($)	Second treatment ($)
Direct — medical	1 127.13	61.49
Direct — patient	393.70	372.90
Indirect	59.22	19.74
Total	1 580.05	454.13

Costs of Selected Hospitalizations Related to Pregnancies

Cost estimates for selected hospitalizations related to pregnancies are presented in Table 22. Because information on direct patient expenses and productivity losses could not be obtained from medical records, all cost estimates are from the perspective of the insurer/payer. They include the cost of staying on the ward and costs incurred from other hospital departments (e.g., medical records and laboratories). These costs are based on a sample of medical charts; more detailed costing for each type of hospitalization can only be obtained from more detailed patient follow-up.

Table 22. Cost of Selected Hospitalizations Related to Pregnancies in 1990

Type of hospitalization	Hospitalized days or short-stay visits	Total estimated cost ($)
Normal vaginal delivery (term pregnancy)	3 days	806.58
Caesarian section	5 days	1 472.75
Ectopic pregnancy	4 days	1 680.38
Spontaneous abortion, miscarriage, and D&C	1 visit	430.49

Discussion

The results of this study must be interpreted and used carefully. Although there were more pregnancies, parturitions, and live births in the experimental group ("IVF treatment") than in the control group ("no IVF treatment"), absolute results, or results expressed on a per-patient basis are misleading if pregnancy or live birth rates are influenced by time at risk. For interventions that are attempted only once and either work or do not work, this is not a problem, but pregnancy rates are influenced by time, because infertile couples may conceive naturally in addition to undergoing assisted reproductive techniques.

When expressed in absolute numbers or rates on a per-patient basis, the results for the experimental group appear to be better than those for the control group. However, these comparisons are confounded, since the experimental group was observed for a longer period than the control group. The influence of the additional months at risk for the experimental

group is substantial. Therefore, expressing pregnancy, parturition, or live birth rates per month at risk, or analyzing them using survival techniques, is needed to assess whether in fact there are better outcomes for the experimental group. When time was incorporated into the analysis in these ways, we found no difference in pregnancy or live birth rates between patients assigned to IVF treatment and those not assigned to treatment. Stricter admission requirements (longer durations of infertility) or longer (placebo) waiting periods may be cost-effective alternatives to immediate IVF treatment; however, the study was not designed to test these specific hypotheses.

Although it can be argued that a pure intention-to-treat analysis is most appropriate for this study, unanticipated scheduling delays in the clinic may have contributed to a bias against the experimental group from the comparison that was originally intended. These unanticipated delays mean that fewer IVF cycles were observed on the experimental group (approximately two per patient who actually started treatment). We examined the impact of this potential bias by redefining the starting date for the evaluation of the patients in the experimental group to the first day of their first IVF cycle (E_{T2}). Given the fact that the pre-treatment pregnancy rates of the experimental and control groups were identical, this redefinition appeared justified. However, it added an eligibility criterion (post hoc ineligibles) to the study that had not been previously stated (i.e., at least one cycle initiated while in the experimental group). More importantly, it did not help to demonstrate a difference between the experimental and control groups in pregnancies, parturitions, and live births, possibly because redefining the starting date for the experimental group meant that the experimental and control groups no longer had identical durations of infertility. If, as the literature suggests, there is a cumulative pregnancy curve for infertile couples that flattens out over time (or over the duration of infertility), then we may be evaluating experimental patients and control patients at different points on the curve. By attempting to counter the influence of one bias against the experimental group, another one may have been introduced.

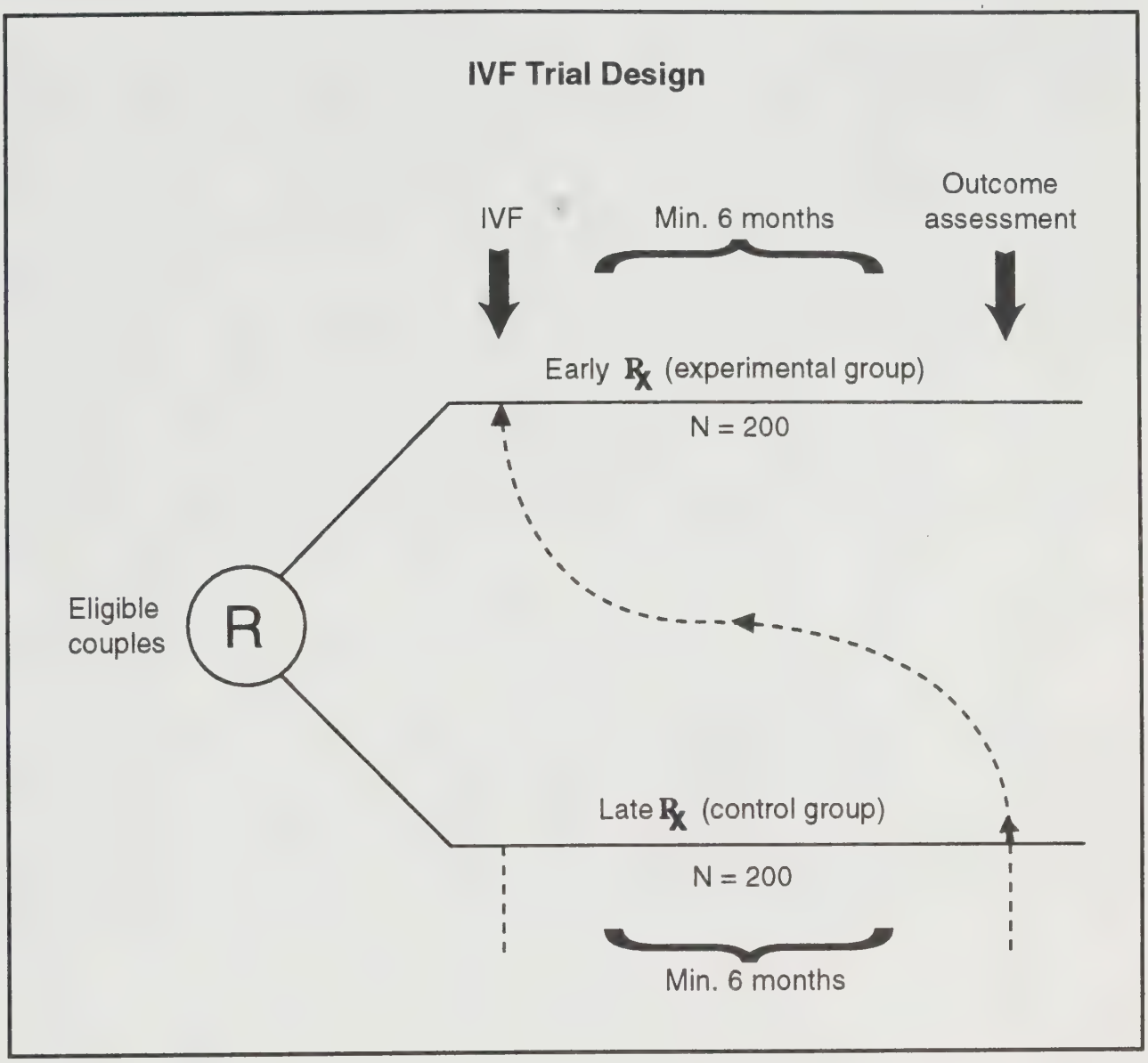
These issues underscore the fact that the results of this study apply to a specific program. An evaluation of this program with tighter controls over the delay before the first treatment or with more IVF cycles per patient over the observation period could yield different results. In this study, only 139 out of the 205 patients assigned to the experimental group received treatment. These patients only received an average of two cycles of treatment over the 14-month period. The study was, therefore, a program evaluation of effectiveness and not efficacy. This distinction is important because it partly explains the difference between the results of this study and success rates reported in other studies. The concern over using these pregnancy and live birth rates is that without a formal comparison with a

control or "no IVF treament" group, the incremental or additional benefits of the IVF program cannot be determined.

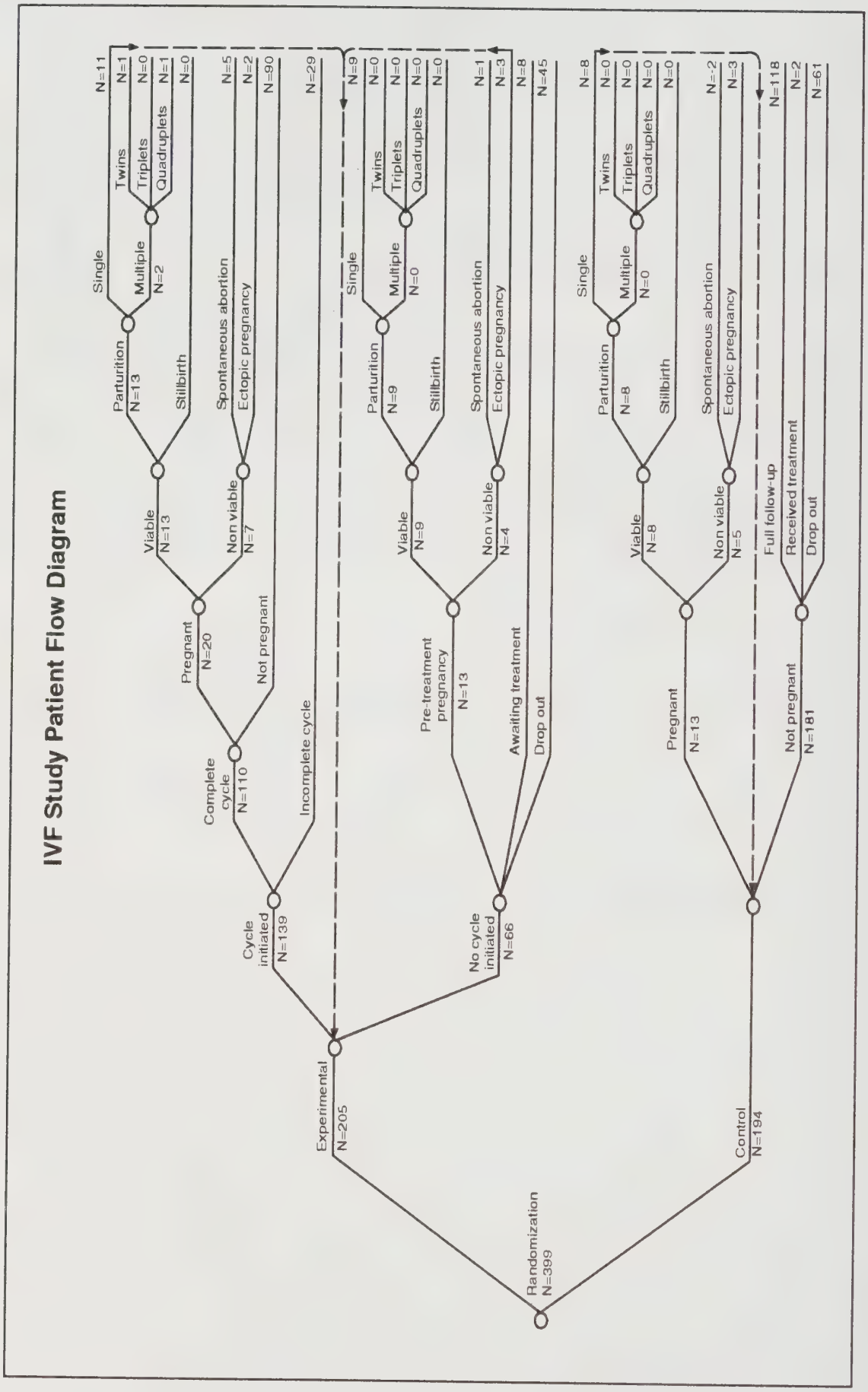
Although not part of the study design, a number of other hypotheses are generated from the study results. The analysis suggests that there is no difference between the two groups' rates of ectopic pregnancies and spontaneous abortions. It also suggests that IVF treatment has better success rates with patients with prior peritoneal disease (tubal disease and endometriosis) than with patients who have other diagnostic types of infertility. And finally, consistent with the anecdotal evidence, the results of this study suggest that there are higher rates of multiple births with IVF treatment. These hypotheses should, however, be evaluated with studies specifically designed to address them.

Finally, it should be noted that the IVF program evaluated in this study is continuously changing. Not only did a number of important changes take place in clinic and treatment protocols during the study, but a number of important changes have taken place since the end of the study (30 April 1990). Although it is always a challenge to evaluate and know when to evaluate, a constantly evolving technology, this should be kept in mind when interpreting and generalizing the results of this study.

Appendix 1.


IVF Trial Design
IVF
Min. 6 months
Outcome assessment
Early Rx (experimental group)
N = 200
Eligible couples
R
Late Rx (control group)
N = 200
Min. 6 months

Appendix 2.


IVF Study Patient Flow Diagram
Randomization
N=399
Experimental
N=205
Cycle initiated
N=139
Complete cycle
N=110
Incomplete cycle
N=29
Pregnant
N=20
Not pregnant
N=90
Viable
N=13
Non viable
N=7
Single
N=11
Multiple
N=2
Parturition
N=13
Stillbirth
N=0
Twins
N=1
Triplets
N=0
Quadruplets
N=1
Spontaneous abortion
N=5
Ectopic pregnancy
N=2
No cycle initiated
N=66
Pre-treatment pregnancy
N=13
Viable
N=9
Non viable
N=4
Single
N=9
Multiple
N=0
Parturition
N=9
Stillbirth
N=0
Twins
N=0
Triplets
N=0
Quadruplets
N=0
Spontaneous abortion
N=1
Ectopic pregnancy
N=3
Awaiting treatment
N=8
Drop out
N=45
Control
N=194
Pregnant
N=13
Viable
N=8
Non viable
N=5
Single
N=8
Multiple
N=0
Parturition
N=8
Stillbirth
N=0
Twins
N=0
Triplets
N=0
Quadruplets
N=0
Spontaneous abortion
N=2
Ectopic pregnancy
N=3
Full follow-up
N=118
Not pregnant
N=181
Received treatment
N=2
Drop out
N=61

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Particular appreciation goes to the methodological consultants, who helped shape and direct the analyses. Major contributors in this regard were George Torrance, Greg Stoddart, Rob Roberts, and Corinne Dulberg.

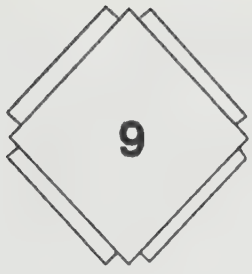
Finally, special mention goes to Mary Helen Blackall, the research nurse; Lori Scapinello, the research assistant; and Sandra Russell, the secretary. Without their persistence, this project would not have been completed.

This report is dedicated to Roberta Labelle, one of the original investigators on the project.

Notes

1. Cost analysis refers to the process of identifying, measuring, and valuing costs to include in an evaluation, and not simply calculating total costs.

2. In cost-effectiveness analysis, the costs and outcomes of alternative interventions are compared. In cost-minimization analysis, because the outcomes of the interventions are similar or identical, only the costs of the interventions are compared.



Public Preferences Toward an *In Vitro* Fertilization Program and the Effect of the Program on Patients' Quality of Life

Ron Goeree, Roberta Labelle, and John Jarrell



Executive Summary

In vitro fertilization (IVF) is a comparatively new treatment for infertility. Advocates of IVF claim that it is worthwhile because of its clinical outcomes, and because it has a substantial impact on patients' quality of life. While the results of clinical and economic evaluations suggest that, overall, the treatment is not effective or is of limited effectiveness compared with no infertility treatment or conventional infertility treatment, the impact of IVF on patients' quality of life has not been formally evaluated. In addition, although IVF is largely publicly financed in the province of Ontario, it is not known what value is placed on it by the general public, although this and other work for the Royal Commission on New Reproductive Technologies (RCNRT) will illuminate this. The authors of the study describe and report the results of a formal investigation of these issues. In doing so they attempt to answer such questions as these: Is expected quality of life different for patients assigned to receive IVF? Does the general public value IVF outcomes to the same degree as do infertile couples? How does the general public value IVF compared with other programs?

This paper was completed for the Royal Commission on New Reproductive Technologies in April 1992.

For the quality of life evaluation, experimental and control groups consisting of 80 subjects each were randomly selected from among patients who were part of a randomized controlled clinical trial of "IVF treatment" and "no IVF treatment" conducted at Chedoke-McMaster's IVF clinic in Hamilton, Ontario during the period 1987-1990. In addition, a community sample consisting of 80 members of the Hamilton-Wentworth community was randomly selected using enumeration lists.

Quality of life was measured using the health utilities approach. The members of all three groups were asked to read a page of information about IVF in order to give them a common basis of understanding. They were then asked to rank potential IVF health outcomes, and these ratings were used to construct a rank ordering. Finally, the respondents were presented with a "chance board" that offered them two options that were assigned various probabilities of occurring — referred to as the "standard gamble" — in order to calculate utility scores.

The researchers use three different methods to analyze the quality of life data for infertile patients. The first is decision analysis, a method used by physicians, policy makers, and researchers to help them make health care decisions under conditions of uncertainty. Second, since IVF typically involves several people, it is important to measure overall changes in quality of life, for all involved, from society's perspective. To do this, the researchers intended to employ Quality Adjusted Life Years (QALYs). Finally, analyses of variance (ANOVA) are conducted to determine whether there is a "program" effect — some administrators claim that IVF has a benefit in and of itself because it allows people to "get on with their lives." In order to determine how members of the general public value IVF, the community sample was asked to rank the outcomes of IVF. They were also asked to rank the necessity and importance of 12 health care programs, including IVF.

Based on a comparison of the utility scores for IVF patients and the community sample, the authors conclude that "there was a significant difference in utility scores between the health outcomes measured." In other words, there was a health outcome effect. Not surprisingly, IVF patients rated non-child health outcomes lower than the community sample did. Based on the decision analysis, the authors conclude that the public's perception of the quality of life improvements rendered by IVF is not different whether the patients participate in an IVF treatment program or not.

Are the objectives of Ontario's IVF program being met? Since the Ministry of Health's objectives are not known, the authors propose three possible objectives: to produce pregnancies, to improve patients' quality of life, and to produce pregnancies *and* to increase patients' quality of life. Based on the results from the wider evaluation of Chedoke-McMaster's IVF program, they conclude that none of these objectives is being met.

Given the findings and current program admission requirements, the authors raise the question of whether the government should continue to finance IVF. The question is reinforced by the finding that a community sample of 80 individuals rated IVF as one of the least necessary of a list of 12 medical programs.

Introduction

In vitro fertilization (IVF) is a relatively new technique that has not been fully evaluated. The only controlled trial of IVF (Goeree et al. 1993) suggests that, overall, the treatment is not effective, or is of limited effectiveness, compared with "no" or "conventional" infertility treatment. Despite these clinical findings, advocates of IVF programs claim that the treatment is worthwhile, not only because of its clinical outcomes, but because it has a substantial impact on patients' quality of life. Until now, no study has formally evaluated this impact. This study attempts to do so in the context of a randomized controlled trial.

Although IVF is publicly financed in the province of Ontario, no attention has been devoted to determining how the general public values it. Important questions that have not been addressed include the following: Does the general public value IVF outcomes to the same degree as infertile couples do? How essential does the general public consider IVF to be, compared with other health care programs?

It can be argued that public policy and decisions about the allocation of public resources should be based on informed public opinion. Therefore, we also surveyed a sample of 80 individuals from the community to determine how they value outcomes from IVF programs and how they feel about IVF programs in general. Public opinion is important and must be considered when decisions are made about whether public financing of IVF should be continued, expanded, or even introduced in other provinces.

Methods

Patient Enrolment and Study Design

Subjects for the quality of life evaluation were randomly selected from a larger pool of subjects enrolled in a randomized, controlled clinical trial of "IVF treatment" versus "no IVF treatment" at Chedoke-McMaster's IVF Clinic in Hamilton, Ontario. Chedoke-McMaster's IVF Clinic is one of nine IVF clinics in Ontario. Its catchment area is all of Ontario; however, the majority of its patients are from the Hamilton-Wentworth and Niagara areas. During a larger controlled trial, 205 couples were randomized to the experimental group ("IVF treatment") and 194 couples were randomized to the control group ("no IVF treatment"). For our study, from these patients, a random sample of 80 experimental-group patients (40 couples) and 80 control-group patients (40 couples) were asked to participate in a quality of life assessment program. The average age of these patients was 32 years.

Patients in both the experimental and control groups were interviewed to elicit their preferences vis-à-vis nine IVF program outcomes. These nine health-profile outcomes are presented in Appendix 1. Only those outcomes

with a high probability of occurring were included in the list of IVF outcomes presented to patients. This was done to shorten the total interview time and because outcomes with low probabilities have only a minor influence on the overall results of the analysis. In addition, during a pilot phase of the project on 40 patients, some of the outcomes were rated equally by patients and, therefore, removed from the list of outcomes to shorten the overall interview time. For example, a successful procedure and losing one child was rated the same as a successful procedure and losing two children. These two factors, a low probability of an outcome occurring and an equivalent outcome rating during pilot testing, explain why some of the more publicized multiple outcomes of IVF were not included in the final list of potential outcomes presented to patients. Both the experimental and control-group patients were interviewed at baseline (i.e., entry into the trial) and six months later. The timing of the utility interviews is presented in Appendix 2.

Community Sample Enrolment

In addition to patients, a random sample of 80 members of the community were interviewed to elicit their preferences regarding the IVF program outcomes. Members of the community were also asked to rank, in terms of necessity, the IVF program in comparison with 11 other health care programs. These health care programs are presented in Appendix 3.

The members of the community sample were initially selected using enumeration lists for the Hamilton-Wentworth area. After an initial letter from the study team, a follow-up telephone call was made and an interview time and date was arranged. A surprising 91 percent of those contacted agreed to participate in the study. The age of the community sample participants ranged from 19 to 81 (mean age was 45) and 39 percent were male. Demographic information for members of the community who refused to participate was not collected.

Quality of Life Measurement Instrument (Health Utilities Approach)

There are a number of alternative approaches to measuring quality of life. The health utilities approach (Torrance 1987) provides a non-disease-specific summary measure of health-related quality of life. The measurement approach is based on utility theory (Von Neumann and Morgenstern 1953), which, despite four decades of criticism, has continued to be the dominant normative paradigm in the field of decision making under uncertainty. This is largely because it is based on a set of simple axioms and is in wide use internationally. Not only have hundreds of books and journal articles been written on the topic, but a whole movement in evaluation and decision making incorporating the approach has emerged (e.g., the Society for Medical Decision Making and its journal, *Medical Decision Making).*

Quality of life measurements for the present study were obtained using a three-step approach. First, experimental-group patients, control-group patients, and members of the community sample were asked to read a one-page preamble (Appendix 4). The preamble was designed to provide a common base of understanding for all respondents. It provided information on IVF treatment and the potential benefits and negative consequences of the intervention.

Second, each group of respondents was presented with a list of nine potential IVF outcomes. They were asked to rate each outcome on a standard scale in which perfect health was assigned a value of 100 and death a value of 0. These ratings were used to construct a rank ordering of IVF outcomes in terms of each respondent's preferences.

Finally, quality of life was measured using a chance board (or probability wheel) to elicit the utilities the respondents placed on each outcome. The chance board is a visual aid instrument where the respondent is asked to select from two possible choices, option 1 or option 2. If chosen, option 2 has a 100 percent probability of occurring, whereas option 1 consists of two alternative health outcomes with the probability of the outcomes occurring dictated by odds or percentages of chance that are varied during the interview. Utility scores depend on the interviewee's choices. Presenting the options to the respondent in this fashion is referred to as the "standard gamble." The "standard gamble" format and an example of an IVF standard gamble are presented in Appendix 5.

Quality of Life Data Analysis

The most appropriate method for analyzing data depends on the questions being asked. Since this study attempted to answer a number of different questions, three main streams of analysis were proposed for examining the quality of life data for patients and members of the community sample. In the following sections, we describe each approach and the questions the analyses were intended to address.

Decision Analysis and Expected Utility

Decision analysis is an approach to making decisions under conditions of uncertainty. Uncertainty in health care decision making arises for a number of reasons, including: uncertainty about the outcomes of treatment; uncertainty about diagnosis and interpretation; uncertainty about compliance; and uncertainty about the perceived benefits of treatment. Decision analysis incorporates these uncertainties and formulates the problem in a systematic way that allows the researcher, physician, or policy maker to decide which course of action should provide the best results.

Using decision analysis we attempted to answer the question, from which course of action (option or branch of treatment) can we expect the best outcome? In the case of IVF, we wished to know which option is expected to give us the best outcome in terms of expected utility (quality of

life). A decision tree is often used to display the temporal and logical sequence of a decision problem. A simplified decision tree associated with the problem comparing "IVF treatment" with "no IVF treatment" is presented in Figure 1.

There are four primary outcomes for the "no IVF treatment" branch or option (C^1 to C^4) and eight primary outcomes for the "IVF treatment" branch or option (E^1 to E^8). Each of these outcomes has a utility value (quality of life measure) associated with it and each branch within the decision tree has a probability of occurring. The probabilities for the IVF decision tree were obtained from a cost-effectiveness analysis conducted in another study (Goeree et al. 1993) and the utility scores for each outcome were obtained from the present study. Multiplying each utility score by the probability of the outcome occurring yields the expected utility of each outcome.

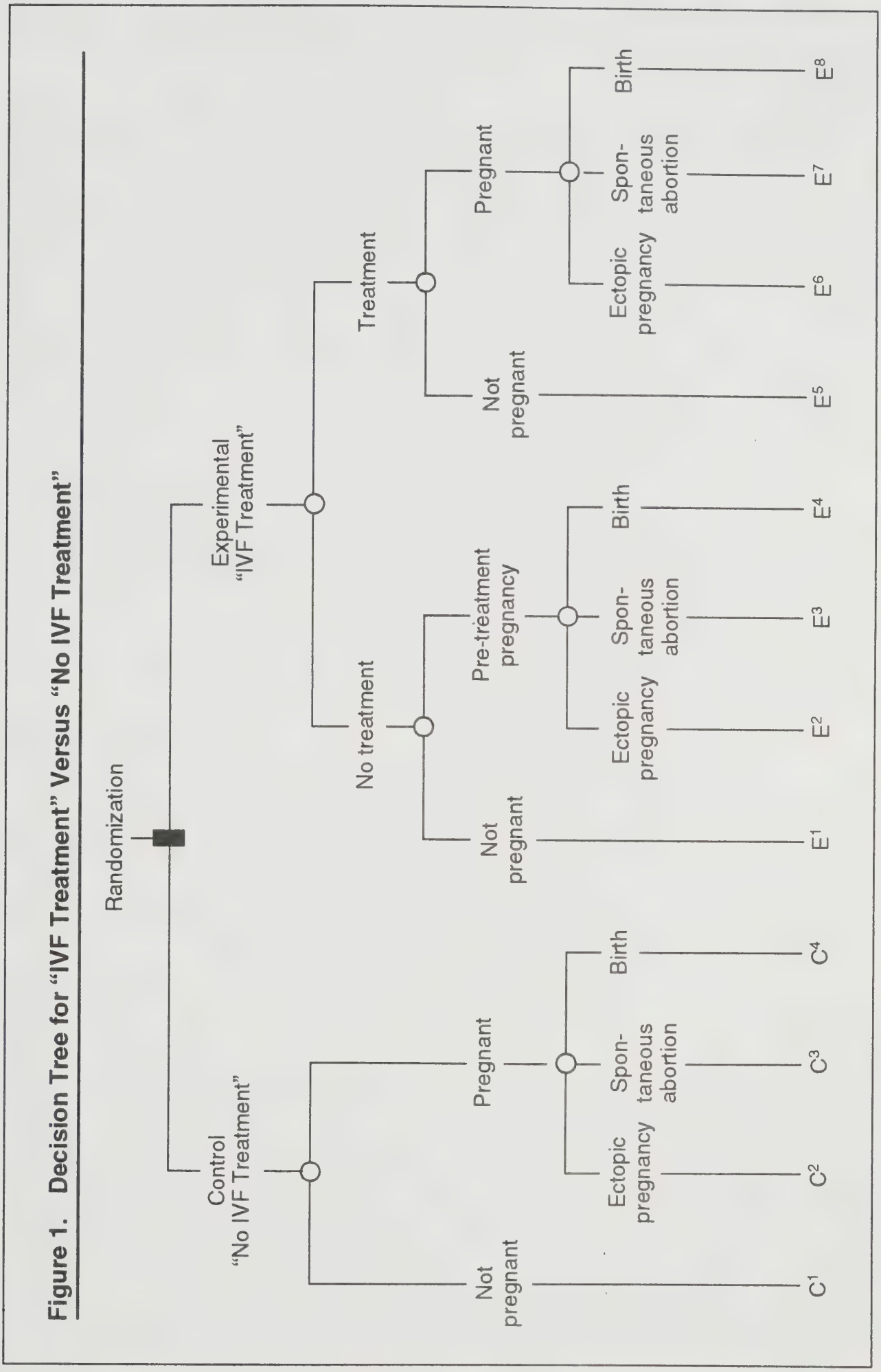
The expected utility of each main branch of the tree ("no IVF treatment" and "IVF treatment") is then determined by multiplying the probability of each outcome by the utility score for that outcome and summing these products across all possible outcomes. The result is an expected utility for each branch of treatment; these can then be compared to determine which branch has the higher expected utility.

Whose utility scores to use in the analysis is a source of debate. Since IVF is largely publicly funded in Ontario and since it can be argued that public decisions should be based on public opinion, the utility scores from the community sample were used for the main analysis. However, since this standard approach is a source of debate, the impact on expected utilities of substituting IVF patient scores for the community sample's utility scores was also investigated. Another source of debate is whether individual utility scores or average group utility scores should be used in the analysis. In this analysis average group utility scores were used, as this is the standard approach in decision analysis.

To determine whether there was a statistically significant difference between the expected utilities for the "no IVF treatment" branch and the "IVF treatment" branch, a technique known as the "Monte Carlo Sensitivity Analysis" was used. Repeated random samples of utility scores from the distribution of utility scores from each health outcome were used to determine the impact on the overall expected utility of each branch. The distributions of each branch's expected utility were then compared using standard *t*-tests to determine whether the mean expected utilities were equal (null hypothesis).

As an alternative and near equivalent test for determining which course of action has the best outcome or highest expected utility, we compared the average change in utility (quality of life) over time in each group. The change in utility over time for each patient was calculated and the average change in utility scores between the control and experimental

Figure 1. Decision Tree for "IVF Treatment" Versus "No IVF Treatment"



groups were compared for equivalence (null hypothesis) using standard *t*-tests. This alternative analysis was also conducted using utility scores for the community sample and for IVF patients.

Total Change in Quality of Life, QALYs, and the Societal Perspective

The objective of decision analysis and expected utility is to determine which course of action has the best outcome (or highest expected utility) for the patients being treated. In the case of IVF, however, there is more than one person involved. The quality of life for the female partner, male partner, and child(ren), if any, are all potentially influenced by the course of action. By adding the change in quality of life for the two (or more) parties involved (and ignoring externalities on other parties), the overall change in quality of life — from society's perspective — can be determined. This change in quality of life can be calculated regardless of whether there is a difference between the expected utilities of the alternative courses of action for the individual patient.

A common method used for calculating overall changes in quality of life is Quality Adjusted Life Years (QALYs). In this approach the utility (quality of life) for each year is multiplied by the number of years expected in that state or with that outcome. These "quality adjusted" years are then added together to determine the total QALYs from each outcome or alternative for each individual. By subtracting the total QALYs from one course of action for all individuals (e.g., control) from another course of action (e.g., experimental), the incremental QALYs gained from one course of action over another is obtained.

Although QALYs are in common use in health care program evaluation and decision making, it should be noted that the use of QALYs is not uncontroversial (Gafni 1989). It has been argued, for example, that valuation of time is already included in the measurement of health outcome utilities, and that assuming these utilities are constant for each year and adding each "quality adjusted year" may be inappropriate. These controversies notwithstanding, however, and in light of their common and widespread use, QALYs were considered for this analysis.

QALYs are typically calculated by multiplying the utility scores for each health outcome by the expected remaining years of life. For example, the average age of patients at entry into the study was 32 years. Using Statistics Canada's life tables (Canada, Statistics Canada 1991), the expected remaining years of life for 32-year-old females is 49 years and for 32-year-old males it is 43 years. In light of the fact that children born to parents in the study had no clearly identified health problems, perfect health (utility of 100) and an average life expectancy of 76 years can be assumed for each child born. Using this information, QALYs for all female partners, male partners, and child(ren), if appropriate, could be aggregated for both the "no IVF treatment" and "IVF treatment" groups.

Before calculating QALYs, however, it is important to determine whether there are statistically significant differences between the health

outcomes (including children born) and utility scores for the two alternatives. Small and non-significant differences in outcomes and/or utility scores could result in differences in total QALYs when multiplied over the expected remaining lifetime of each male partner, female partner, and child born. Therefore, tests of significance were conducted before QALYs were calculated.

Change in Utility Scores — The Program Effect

The third category of analysis attempts to answer the question, "Was there a program effect?" One of the specific hypotheses tested was, "After receiving IVF treatment, did the patients change their relative preference for unsuccessful outcomes?" Some administrators have claimed that treatment allows patients to "believe they have done everything they could," and allows them to "get on with their lives." Perhaps in this way IVF treatment has a benefit in and of itself. To test this hypothesis, the following three comparisons were conducted (see Appendix 2 for the timing of the utility interviews):

1. experimental and control groups at baseline;
2. experimental group before treatment (baseline) and after treatment (six month follow-up, i.e., the change over time); and
3. control group at baseline and six-month follow-up (i.e., the change over time).

The justification of and approach used for each of these comparisons are discussed below.

Comparison of Experimental and Control Groups at Baseline

This comparison was conducted to test whether there were any systematic differences between the two groups at entry into the study.

Comparison of Experimental Group Before Treatment (Baseline) and After Treatment (Six-Month Follow-up i.e., the Change over Time)

This comparison was used to test some of the hypotheses put forward by administrators regarding the benefits of IVF treatment.

Comparison of Control Group at Baseline and Six-Month Follow-up (i.e., the Change over Time)

Comparing how the control group changed over time served as a control to changes observed in the experimental group. Both groups may have been affected by internal factors (e.g., changing preferences as a result of age) or external factors (e.g., events in the media). Without the control group, factors unrelated to the impact of IVF treatment itself might have gone undetected when examining how experimental couples' valuation of outcomes changed over time.

For all three comparisons, repeated-measures analysis of variance (ANOVA) tests were used to test for overall group effects (i.e., differences between groups or across time within groups), overall IVF health outcome

effects (i.e., differences in rating of health states H1 to H13), and overall interaction effects. Overall group effects measure differences between the utility scores of the groups being compared, regardless of differences between health outcomes. Overall health outcome effects measure differences between the utility scores for IVF health outcomes, regardless of differences between groups. And finally, overall interaction effects measure the interaction between the two main effects. Two-way ANOVA tests were then conducted on specific comparisons where group, health outcome, or interaction effects were significant. This was used to help identify which variables influenced the overall effects.

Community Sample Health-Care-Program Rating Instrument (Rating Scale Approach)

Eighty individuals from the community were asked to rank, in order of necessity and importance, 12 health care programs, including IVF treatment (see Appendix 3). The health care programs were ranked on a 0-100 visual analogue scale, where 0 represented the least necessary and 100 the most necessary. To assist in the rank ordering, respondents were encouraged to rank programs equally if they felt the programs were equally necessary.

Community Sample Rating-Scale Data Analysis

Since the respondents were asked simply to rank the programs in order of preference, only ordinal measurements were obtained for the health care programs. In addition, since the scale did not have pre-defined, standardized upper or lower bounds for all respondents, traditional methods of describing or analyzing the data (e.g., means, variances, and ranges) were not appropriate. Therefore, the results of the program ranking by the community sample were described according to the relative ranking by each individual. The number of times each program was ranked first, in the top three, in the bottom three, and last was calculated.

Results

Experimental Group, Control Group, and Community Sample Utility Scores for IVF Health Outcomes

The mean scores for each of the nine IVF health outcomes for the baseline (T1) and six-month follow-up (T2) utility interviews are presented in Table 1. The mean scores for the community sample (T1) and for the control and experimental groups combined (T1) are presented in Table 2. All utility scores are expressed on the standard 0-100 (death-perfect health) scale. Using repeated-measures ANOVA tests, the following five comparisons were conducted for overall group effects (i.e., across groups or across

time within groups), overall IVF health-outcome effects (i.e., H1 to H13), and overall interaction effects (i.e., the interaction between the two main effects):

1. experimental and control groups at baseline;
2. experimental group before treatment (baseline) and after treatment (six month follow-up);
3. control group at baseline and six-month follow-up;
4. experimental and control groups at six-month follow-up; and
5. combined experimental and control groups at baseline and community sample.

To identify which variables were main contributors to any overall group, health outcome, or interaction effects, two-way ANOVA tests were used for specific comparisons. The results of these analyses are discussed in the following five sections.

Table 1. Mean Utility Scores for IVF Patients, by Interview and Health Outcome

	Experimental		Control	
IVF health outcome*	Baseline (E_{T1}) n = 81	6 Months (E_{T2}) n = 71	Baseline (C_{T1}) n = 71	6 months (C_{T2}) n = 64
H1	99.91	98.97	96.87	99.21
H2	96.53	95.63	94.70	96.20
H3	97.45	93.96	96.75	94.67
H5	68.33	65.91	62.99	66.69
H7	69.23	65.89	61.25	67.84
H9	65.80	62.62	59.89	64.11
H11	66.29	62.15	59.42	65.85
H12	70.30	66.28	61.79	67.46
H13	69.49	65.05	60.83	65.43
Death	0	0	0	0

* See Appendix 1 for description of health outcomes.
T1 - baseline
T2 - 6-month follow-up
n - number of patients

Table 2. Combined IVF Patient Mean Utility Scores and Community Sample Mean Utility Scores, by Health Outcome

IVF health outcome*	Combined IVF patients (EC_{T1}) n = 152	Community sample (CS_{T1}) n = 80
H1	98.49	100.00
H2	95.68	97.50
H3	97.13	96.72
H5	65.84	81.84
H7	65.50	79.35
H9	63.04	65.79
H11	63.08	70.56
H12	66.33	81.21
H13	65.44	81.89
Death	0	0

* See Appendix 1 for description of health outcomes.
EC - Experimental and control groups
n - number of respondents

Comparison of Experimental and Control Groups at Baseline (E_{T1} vs. C_{T1})

This comparison demonstrated overall group and health outcome effects. Therefore, not only was there a significant difference between utility scores for different IVF health outcomes ($p < 0.01$), but there was also an overall significant difference between the experimental and control groups at baseline ($p < 0.01$). Although the health outcome effect was expected, the group effect was not, given the randomized design of the study. Experimental-group patients at baseline (E_{T1}) rated all IVF health outcomes slightly higher than did control-group patients at baseline (C_{T1}) (Table 1). Two-way ANOVA tests failed to demonstrate any significant differences between the experimental and control groups on individual IVF health outcomes. It should be noted, however, that the higher experimental-group ratings for the non-child IVF health outcomes (i.e., H5, H7, H12, and H13) approached statistical significance.

Comparison of Experimental Group at Baseline and Six Months (E_{T1} vs. E_{T2})

This comparison demonstrated a health-outcome effect only ($p < 0.01$). Overall, there were no significant differences between the experimental group's utility scores for each health outcome over time.

Comparison of Control Group at Baseline and Six Months (C_{T1} vs. C_{T2})

This comparison also demonstrated a health-outcome effect only ($p < 0.01$). Overall, there were no significant differences between the control group's utility scores for each health outcome over time.

Comparison of Experimental and Control Groups at Six Months (E_{T2} vs. C_{T2})

This comparison demonstrated a health outcome effect only ($p < 0.01$). Overall, there was not a significant difference between the experimental and control groups' utility scores at six months.

Comparison of Combined Experimental and Control Groups at Baseline and the Community Sample (EC_{T1} vs. CS_{T1})

This comparison demonstrated overall group effects ($p < 0.01$), health outcome effects ($p < 0.01$), and interaction effects ($p < 0.01$). With the exception of one outcome, the community sample (CS_{T1}) consistently rated all IVF health outcomes higher than did the IVF patients (EC_{T1}) (Table 2). This higher rating applied to both child outcomes (i.e., H1, H2, H3, H9, H11) and non-child outcomes (i.e., H5, H7, H12, H13). Two-way ANOVA tests demonstrated that the non-child outcomes explained most of the overall group effect. All four non-child outcomes were rated significantly higher by the community sample ($p < 0.01$).

Decision Analysis and Expected Utility

Using a decision tree (Figure 1), the branch probabilities from a cost-effectiveness analysis conducted previously (Goeree et al. 1993) and average group utility values for the community sample (CS_{T1}) and all IVF patients (EC_{T1}), the expected utilities for "IVF treatment" and "no IVF treatment" were calculated (Table 3). .

Table 3. Expected Utility Using Utility Scores for the Community Sample (CS_{T1}) and IVF Patients* (EC_{T1})

	Community sample	IVF patients
"IVF treatment" (experimental) branch	82.8	68.6
"No IVF treatment" (control) branch	82.6	66.8
Net expected utility	0.2	1.8

* Based on experimental and control group's pooled scores.

The results of the Monte Carlo Sensitivity Analysis and the analysis of the average change in overall utility over time both corroborate the finding of no significant difference in expected utility between the "IVF treatment" and the "no IVF treatment" branches when average group utility scores for the community sample are used. In other words, given the program's

outcomes, the benefit to patients in terms of quality of life improvement as perceived by the community sample is not expected to be different whether patients participate in an IVF treatment program or not. This finding is also upheld when patient utility scores are used.

Quality Adjusted Life Years (QALYs)

The results of this analysis and the cost-effectiveness analysis (Goeree et al. 1993) suggest that there were no statistically significant differences in pregnancy rates, parturitions, or expected utility between the "IVF treatment" and "no IVF treatment" groups. Therefore, the calculation of QALYs is inappropriate and has not been included in this analysis.

Change in Utility Scores — The Program Effect

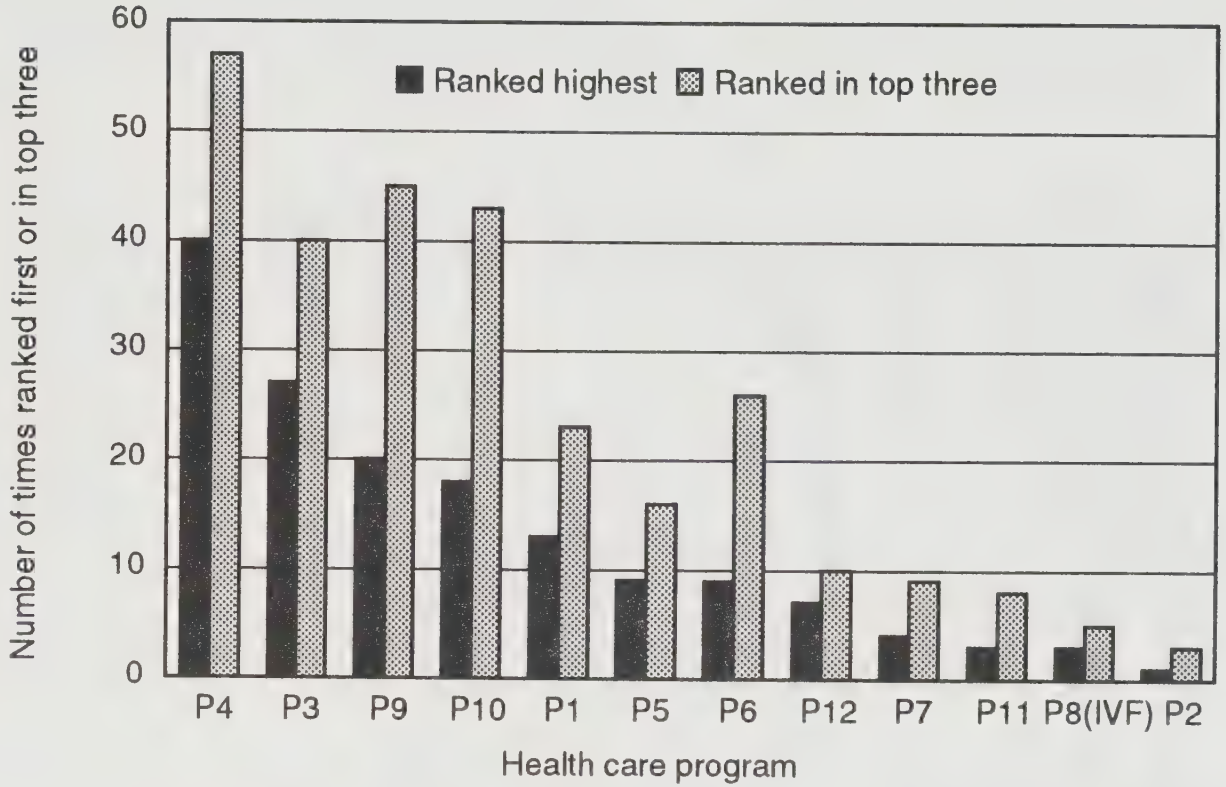
The results of the comparison of the experimental and control groups at baseline (E_{T1} vs. C_{T1}), six months (E_{T2} vs. C_{T2}), and over time (E_{T1} vs. E_{T2} and C_{T1} vs. C_{T2}) did not provide any evidence for the hypothesized "program effect" for experimental-group patients over time. Experimental group patients' ratings of IVF health outcomes that included successful or unsuccessful treatment (i.e., H2, H3, H5, H7, H9, H12) did not change after receiving treatment. There was no overall health-state effect over time using repeated-measures ANOVA tests and no difference within individual health states over time using two-way ANOVA tests. Since there were no differences in health-state ratings over time for the experimental-group patients it was not necessary to compare experimental-group changes over time with control-group changes over time.

Although these findings did not provide evidence for the hypothesized "program effect," it should be noted that the second utility interview was only six months after the first interview and approximately five months after the first IVF treatment. The impact of additional IVF treatment attempts or utility interviews taken later than five months after treatment could not be assessed with the current study design.

Community Sample Health-Care-Program Ranking

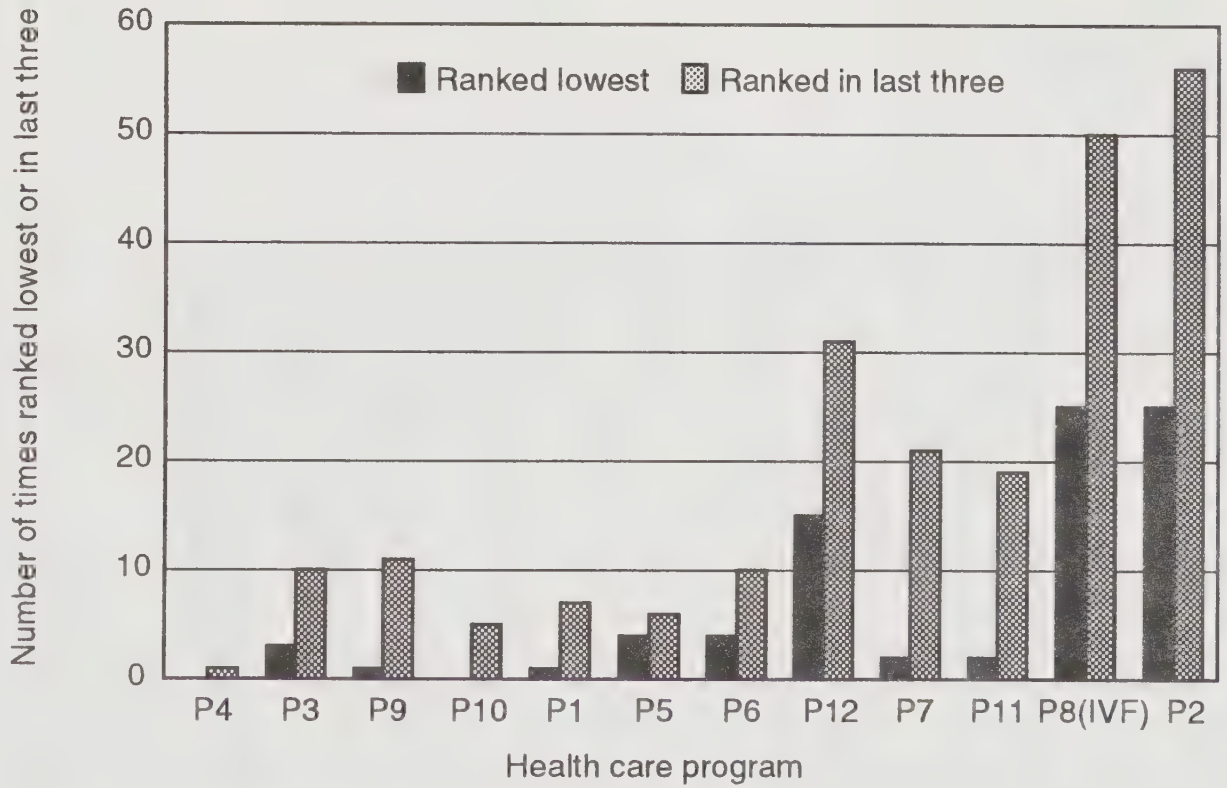
As previously mentioned, the absence of pre-defined, standardized upper and lower bounds for the health-care-program rating instrument meant that traditional methods of describing or analyzing the data (e.g., means, variances, ranges) could not be used. The number of times each health care program was ranked highest by members of the community sample and the number of times each health care program was ranked among the top three health care programs is presented in Figure 2. The number of times each health care program was ranked lowest or among the bottom three by members of the community sample is presented in Figure 3.

Figure 2. Top Priority Rankings by the Community Sample of Selected Health Care Programs



P4 Childhood cancer treatment centres
P3 School immunization programs
P9 Heart bypass surgery
P10 Kidney transplant programs
P1 Home care programs
P5 Other (self-defined)
P6 Nursing home beds
P12 AIDS hospices
P7 Psychiatric day-care
P11 Rape crisis centres
P8 IVF program
P2 Prenatal classes

Figure 3. Lowest Priority Rankings by the Community Sample of Selected Health Care Programs



P4 Childhood cancer treatment centres
P3 School immunization programs
P9 Heart bypass surgery
P10 Kidney transplant programs
P1 Home care programs
P5 Other (self-defined)
P6 Nursing home beds
P12 AIDS hospices
P7 Psychiatric day-care
P11 Rape crisis centres
P8 IVF program
P2 Prenatal classes

Although it is only an ordinal rating scale, a clear conclusion can be drawn from it. With the exception of prenatal classes (P2), IVF (P8) was deemed the least necessary of the health care programs. Only one member of the community sample felt IVF was most important, 25 ranked IVF as the least necessary, and 50 out of the 80 ranked IVF among the three least necessary programs.

Conclusions

The evaluation of utility scores for both IVF patients and members of the community sample indicates that there was a significant difference in utility scores between the health outcomes measured (i.e., health outcomes were rated differently or there was a health-outcome effect). In addition, IVF patients consistently rated all non-child health outcomes lower than did members of the community sample (i.e., there was a strong group effect). This latter finding is not surprising, given IVF patients' strong commitment to having a child.

The results of the decision analysis, however, were not expected. They show that there were no statistically significant differences in expected utility between the "IVF treatment" branch and the "no IVF treatment" branch when the average group utility scores for patients or the community sample were used. In other words, in light of the program's outcomes, the community sample's perception of the benefit to patients — in terms of quality of life improvement — is not expected to be different whether the patients participate in an IVF treatment program or not.

Finally, the results from the ranking of health care programs by members of the community sample indicate that IVF was consistently rated next to the least necessary of the 12 health care programs considered, the only one rated lower being prenatal classes.

Discussion

Advocates of IVF programs claim that IVF has a substantial impact on patients' quality of life in at least two major respects. First, since infertility is not a problem that directly affects the physical health of the patient, successful outcomes of treatments can be viewed primarily as improvements in quality of life. These improvements in quality of life supplement the indirect impact on health, through reduced stress and other emotional effects, that successful outcomes of treatment may have. Second, the impact of IVF treatment on quality of life may not be confined solely to successful outcomes. It has been suggested, for example, that unsuccessful treatment may improve quality of life because couples believe they have "done all they could" to get pregnant and this allows them to "get

on with their lives." Because of the changes in quality of life that result from successful treatment outcomes and from the reassurance and resolution that results from even unsuccessful treatment, advocates of IVF treatment contend that the "success" of IVF should not be measured simply by counting the number of babies born. They claim that an assessment of the *total* benefits of IVF must also include an assessment of the changes in quality of life that result from the intervention.

Before doing so, however, it is important to ask who is funding the program and what the objectives of the program are. With the exception of the medications required, IVF programs in Ontario are financed entirely by public funds. However, the specific objectives of the program from the Ministry of Health's perspective are unknown. Are they to correct infertility, create children, increase quality of life, or some combination of the three? Since the specific objectives of IVF programs are unknown, it is impossible to determine whether the objectives are being achieved. However, we speculated about three possible objectives of an IVF program: to produce children; to increase quality of life for infertile couples; and to produce children *and* increase the quality of life for infertile couples. Using the results from the evaluation of Chedoke-McMaster's IVF program (Goeree at al. 1993), the extent to which these objectives are being met is discussed below.

If the objective of IVF programs is to produce children — or more specifically, to produce pregnancies — regardless of quality of life changes, then the results of the cost-effectiveness analysis of IVF (Goeree et al. 1993) suggest that this objective is not being met. This evaluation showed that for a specific IVF program "IVF treatment" is not effective, or of limited effectiveness, compared with conventional treatment or "no IVF treatment."

If the objective of IVF programs is to increase the quality of life for infertile couples, then the question of whose utility scores should be used, or who should value the quality of life for individual patients, becomes important. The results of this evaluation demonstrated that the community sample rated IVF health outcomes significantly higher than did IVF patients, and that most of this difference was explained by higher ratings for the non-baby health outcomes. This difference in average utility scores between the community sample and IVF patients, however, had little impact on the results of the decision analysis. There were no statistically significant differences in terms of expected utility between the "IVF treatment" and the "no IVF treatment" branches for a specific IVF program when average group utility scores were used.

The results of comparing IVF patient scores over time for a specific IVF program failed to provide support for the second hypothesized source of quality of life improvement, that is, a "treatment effect" due to IVF. Therefore, if the sole objective of IVF programs is to increase patients' quality of life, it appears that this objective also is not being achieved when average group utility scores from a community sample are used.

It is important to emphasize that using average group utility scores requires that one accept assumptions about the comparability of the measurement scales among individuals. Using individual utility scores rather than group utility scores is another alternative, but one that is not standard practice in decision analysis. The implications of, and results obtained from, using individual utility scores will be investigated in a separate analysis (Gafni et al. 1992).

Finally, if the objective of IVF programs is to produce children *and* increase quality of life, then it is obvious that this objective is not being met either, since neither of the individual objectives are being achieved — at least by Chedoke-McMaster's IVF program. The extent to which these objectives could be met by other IVF programs (i.e., those with stricter admission criteria, who accept only patients with tubal factor infertility) is uncertain.

The results of this analysis suggest that, when using average group utility scores (which is the current practice) and from a public decision-making perspective, none of the three objectives (i.e., to produce children; to increase quality of life; or to produce children *and* increase quality of life) is being achieved by Chedoke-McMaster's and possibly other IVF programs in Ontario. This does not necessarily mean that IVF treatment should be discontinued, however. This finding simply raises the question of whether IVF should continue to be publicly financed or whether it should be privately financed. For example, the presenting couple could be asked, "Are you willing to pay $5 000 (i.e., $1 000 in medications plus $4 000 in treatment costs) to receive one IVF treatment, where the success rate is no better than conventional treatment?" The couple would then decide whether the chance of a successful outcome, however success is defined by them, was worth the financial outlay.

Some have suggested that a "private pay" policy like that of cosmetic surgery and non-approved drugs for the elderly should therefore be adopted. With increasing financial pressure on the health care system, this policy is likely to be extended to other health care services in the future, especially those whose effectiveness is questionable or limited. However, it is important to realize that due to the asymmetry in the information possessed by the provider (i.e., the physician) and the consumer (i.e., the patient), "private pay" policies or recommendations leave infertile people open to exploitation because of their desire to have children. Information regarding treatment options, success rates, side-effects, and other potential effects on quality of life would have to be presented to the consumer in a comprehensive and unbiased fashion, and this is unlikely if there is a conflict of interest by the provider, who will benefit if treatment is chosen.

Lending additional support for an alternative financing policy for IVF is the finding that the community sample rated IVF, compared with other health care programs, as one of the least necessary programs. IVF competes for the same public funds as some of the programs that were consistently rated among the most important. From a public

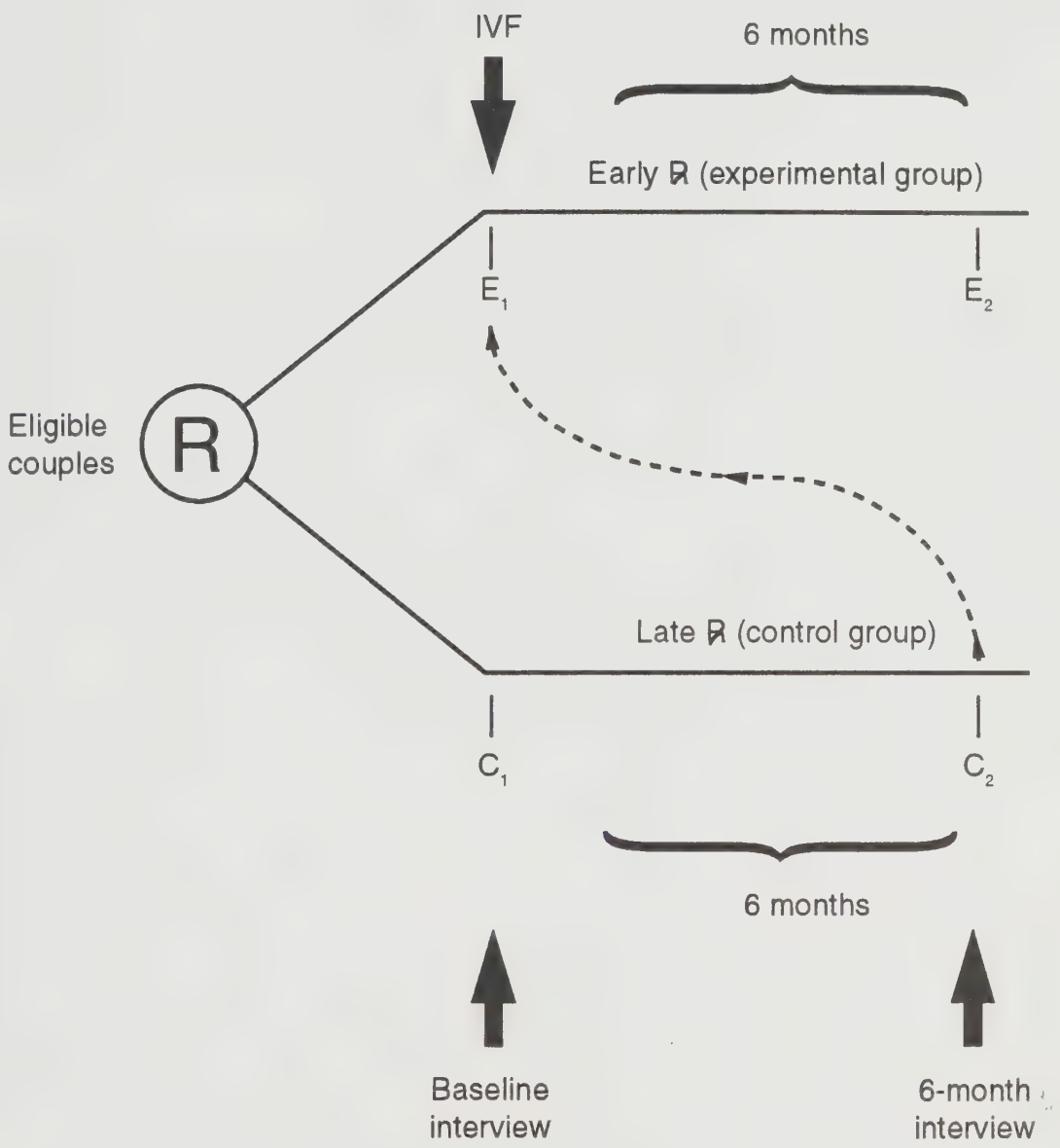
decision-making perspective, it is important to know how the public feels about IVF in general and in comparison with other health care programs. There is a need to move toward incorporating these feelings into equitable and rational public policy for many medical care programs, including IVF.

Appendix 1. List of Health Outcomes

H1 - No procedure, spontaneous pregnancy, healthy child
H2 - Successful procedure, single pregnancy, healthy child
H3 - Successful procedure, twin pregnancy, both healthy
H5 - Successful procedure, single pregnancy, miscarriage
H7 - Successful procedure, ectopic pregnancy, remain childless
H9 - Successful procedure, single pregnancy, moderate to severe handicap or health problem
H11 - No procedure, spontaneous pregnancy, moderate to severe handicap or health problem
H12 - Unsuccessful procedure, no pregnancy, remain childless
H13 - No procedure, no pregnancy, remain childless

Appendix 2. Timing of Utility Interviews

Figure 2A. Timing of Utility Interviews



Appendix 3. List of Health Care Programs

P1 - Home care programs
P2 - Prenatal classes
P3 - School immunization programs
P4 - Childhood cancer treatment centres

P5 - Other (self-defined)
P6 - Nursing home beds
P7 - Psychiatric day-care
P8 - IVF program
P9 - Heart bypass surgery
P10 - Kidney transplant programs
P11 - Rape crisis centres
P12 - AIDS hospices

Appendix 4. Utility Interview Preamble

You (your wife) are (is) under 38 years of age. You and your husband (wife) have been trying, unsuccessfully, to have a child for over two years. During this time, both of you received professional advice in determining the causes of, and the possible treatments for, your infertility. You and your husband (wife) have undergone some or all of these treatments and are convinced it is unlikely that these conventional methods will result in a pregnancy. In response to your infertility, you and your husband (wife) may have experienced feelings of emptiness, incompetence, or depression. These feelings may have affected your home life, your marriage, your work performance, other daily activities, or how you interact socially.

In consultation with your physician, you and your husband (wife) were informed about the *in vitro* fertilization (IVF) program. Through discussions with IVF program physicians and nurses, you and your husband (wife) acquired additional information on the program's treatment and discovered that you met the program requirements. You have learned that the program has a success rate of about one in ten. Of those pregnancies, there is an increased chance of multiple and/or premature births. The increased chance of multiple and/or premature births also carries increased health risks to you (your wife) and your child. However, since the procedure is relatively new, the exact probabilities of these health risks are not known. Nevertheless, after weighing the risks and benefits of the program, you and your husband (wife) have decided to participate.

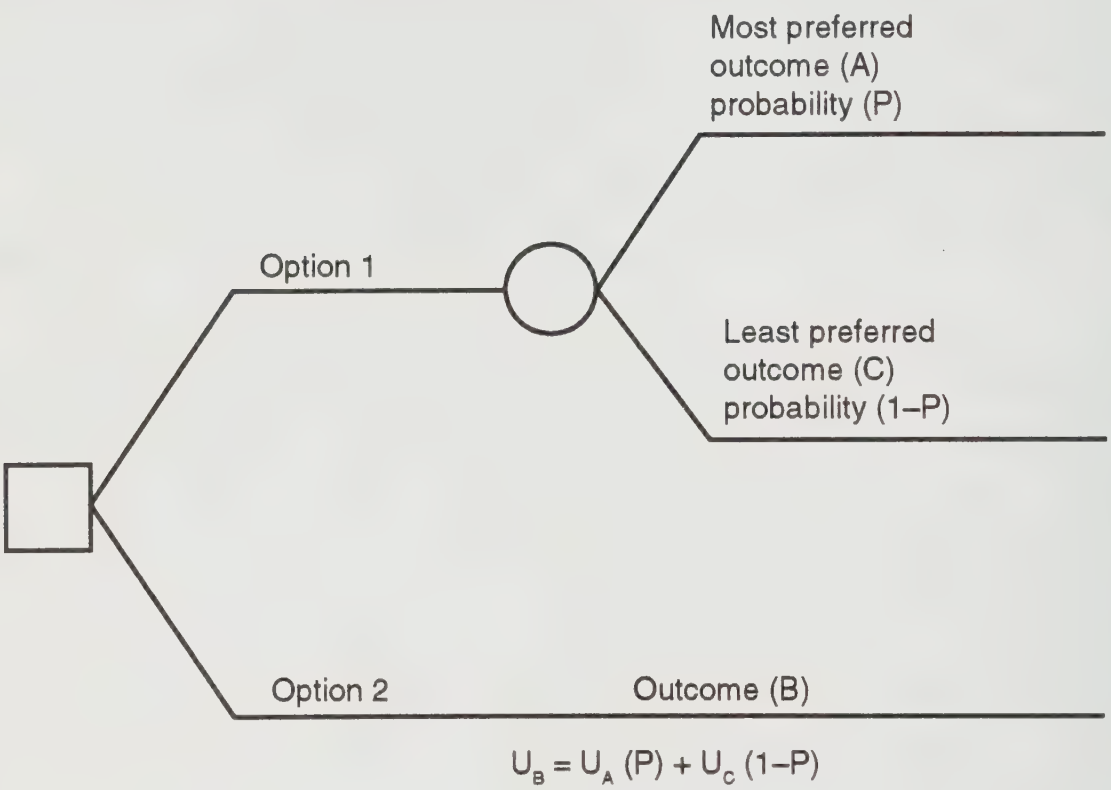
The procedure itself is completed within one month, at which time you will know whether or not you (your wife) are (is) pregnant. During the first two weeks the program is quite demanding. You (your wife) must take pills for five days and come into the hospital every day for one week to receive injections, have ultrasounds (similar to an X-ray), and give blood samples. Your husband (you) must also come in for a semen analysis. During the third week you (your wife) will undergo a laparoscopy (a minor surgical procedure to retrieve your [her] developed eggs) and a few days later an embryo transfer (to return the fertilized eggs). For each procedure, you (your wife) will spend a few hours in the recovery room but will be discharged from the hospital the same day. Both procedures will involve

some pain or discomfort, but you (she) should be able to resume normal activities the next day. The final two weeks will involve two more blood samples and several days' wait to see if menstruation occurs.

Now, you will be asked to consider some hypothetical outcomes of IVF. You should assume that you and your husband (wife) will participate in the program only once and that you will spend your remaining years in the situation described or implied by the outcome. Try to consider to what extent these outcomes might affect you emotionally, your marriage, your day-to-day functioning, or how you interact socially. Please remember that the outcomes we describe are only hypothetical, and many of them have only small probabilities of actually occurring.

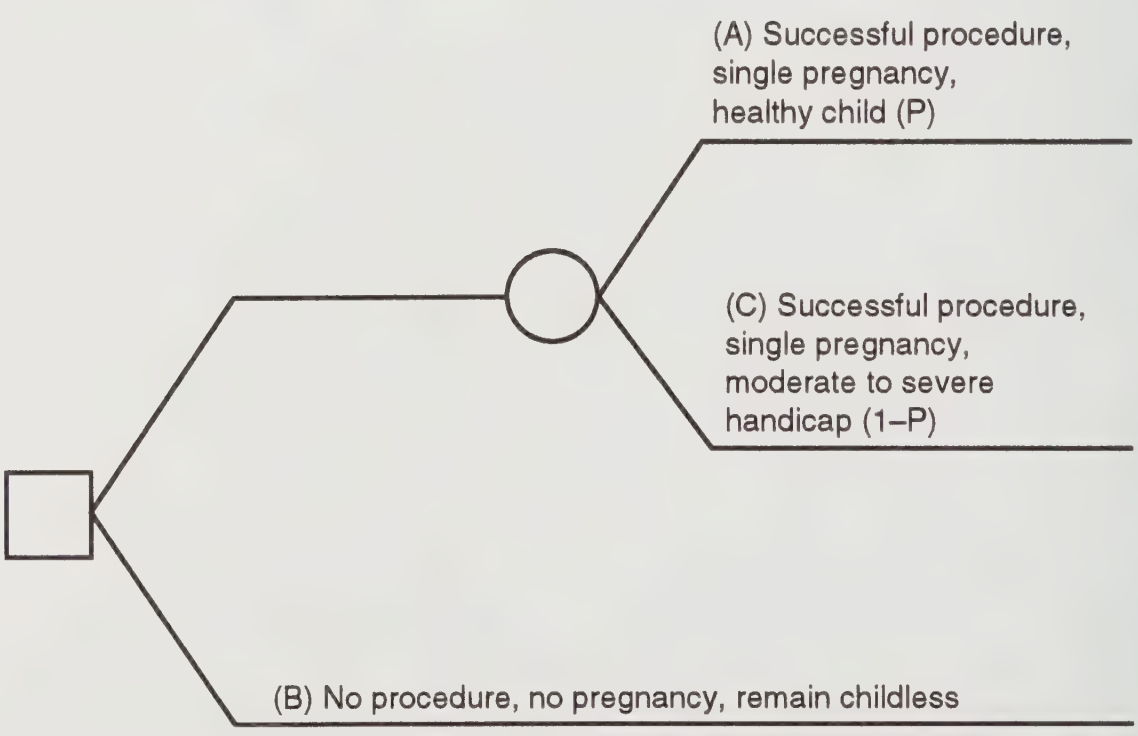
Appendix 5. The Standard Gamble

Figure 5A. The Standard Gamble Format



$$U_B = U_A (P) + U_C (1–P)$$

Example of an IVF Standard Gamble Question*



* In this example A is preferred to B, which is preferred to C.

Acknowledgments

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Finally, special mention goes to Mary Helen Blackall, the research nurse and interviewer, and Lori Scapinello, the research assistant. Without their help, this project would not have been completed.

This report is dedicated to Roberta Labelle, one of the project's original investigators.

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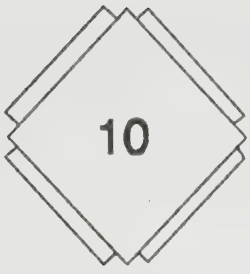
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The Child Health Study: Record Linkage Feasibility of Selected Data Bases: A Catalogue

Lynda Hayward, Darlene E. Flett, and Christine Davis,
The Flett Consulting Group Inc.



Executive Summary

This study reports on the results of an investigation of Canadian data bases that have potential for linking records relating to maternal and paternal infertility risk factors, treatments, and diagnostic procedures with records pertaining to the health of the children of these parents.

The advantages and disadvantages of record linkage methodology are discussed, along with a number of issues associated with the study of risk factors and reproductive outcomes. The data bases were assessed and are classified according to whether they have high, good, possible, or poor record linkage potential.

A catalogue which describes the general and technical characteristics of the data bases and how they may be accessed is included in the study. The catalogue is intended for the use of government agencies, researchers, corporations, interest groups, and data base guardians wishing to expand their research potential.

This paper was completed for the Royal Commission on New Reproductive Technologies in May 1993.

The study concludes that record linkage as a research method can significantly advance knowledge of the relationships between child health outcomes and parental exposure to infertility risk factors, some fertility treatments, and diagnostic procedures.

Introduction

During the public hearings of the Royal Commission on New Reproductive Technologies, the lack of information concerning short- and long-term effects of these technologies on the health of women and the children they bear was a recurring theme.[1] To address this concern, the Commission has initiated research into various risk factors associated with infertility, including the adverse effect these risk factors may have on child health. The risk factors the Commission has studied include sexually transmitted diseases, contraceptive use, occupational and environmental hazards, psychological factors, weight and eating disorders, age, substance abuse, endometriosis, prescription drug use, and iatrogenic causes.

In Canada, only limited use has been made of record linkage methodologies whereby various exposures of parents to such risk factors can be linked to child health outcomes.[2] As the National Task Force on Health Information has pointed out, there is a "bewildering complexity of factors that *may* be significant to health," and no one data base is likely to be sufficient for effective analysis.[3] The data already accumulated in relevant data bases exist in different places scattered across the country and need to be identified and assessed for linkage possibilities.

This project examines the potential for the record linkage of selected Canadian data bases containing maternal and paternal infertility risk factors, treatments, and infertility diagnostic procedures with data bases pertaining to the child's health. Given the time limitations of this study (four months from conception to completion), this document was not designed to be an exhaustive study of the record linkage potential of all Canadian data bases relevant to the study of reproductive outcomes; rather, its purpose is to demonstrate the possible utility of the research methodology, to identify a number of relevant data bases that show some record linkage potential, and to supply enough information to encourage policy makers and researchers to pursue these possibilities. With these goals in mind, a catalogue has been produced, with accompanying documentation, to meet the needs of a diversity of potential users, such as the following:

- various government agencies with specific policy questions that could be addressed by linking available data;
- researchers wishing to do secondary analysis of existing data;

- corporations or interest groups, such as unions, wishing to do a medical follow-up on their members with a view to long-term outcomes;
- researchers wishing to link their own data to such data bases; and
- data base guardians wishing to expand the research potential of their data bases.

Taking into consideration potential users' differing backgrounds and familiarity with record linkage as a research methodology, this catalogue has been organized to facilitate use at a variety of levels.

Content of Document

This document has six sections:

1. an introduction;
2. a general discussion of the record linkage methodology, including its advantages and disadvantages, special issues related to new reproductive technologies, and data base descriptors relevant to the assessment of record linkage potential;
3. a description of how data bases were selected and information about them collected;
4. a discussion of the assessment of the record linkage potential of the data bases, including a description of the criteria used;
5. a set of cross-referencing charts that lists the selected data bases by record linkage group, summarizes their characteristics in terms of the various criteria of assessment, and notes the page of the more detailed description; and
6. a catalogue that includes alphabetically ordered summary descriptions of the data bases.

The section on record linkage has been included for those users who may not be familiar with record linkage as a research methodology and/or with special issues associated with the study of risk factors and reproductive outcomes, specifically the child's health.

The selection of the data bases and the collection of the information describing the data bases has been briefly summarized under "Data Collection Methodology" to help the user understand the origin of the information and the related limitations of this document.

The assessment of the record linkage potential of the selected data bases includes the criteria of assessment and the potential of the various data bases. In this section, the data bases are divided into four groups: those with high, good, possible, and poor record linkage potential.

The fifth section contains summary charts of the data bases by record linkage potential group, cross-referenced to the data base descriptions that follow them. It was designed to facilitate the quick identification of data bases that may be of interest to the user, giving the pages where the more detailed descriptions can be found. It is expected that once users are familiar with the background of this project, they will frequently turn directly to this section.

The final section includes summary descriptions of the data bases. These descriptions have been arranged in alphabetical order so that a data base may be found quickly and directly by name, without consulting the cross-referencing charts.

Record Linkage

Record linkage is basically the process by which the information concerning an individual in one record is linked to information concerning the same individual in another record, by matching common identifying information such as name, sex, date of birth, and address. This could involve either the internal linking of events regarding an individual (such as doctor visits) into a case history within a data set, or the linking of information concerning the same individual contained in two different data bases. Matching can be done in two ways: *deterministic*, where all identifying variables are exactly matched, and/or *probabilistic*, in which some variables match and the probability that it is the same person is within prescribed limits. There is some controversy concerning the relative advantages of the two. However, it may be argued that deterministic matching is a specific case of probabilistic matching in which the probability of a mismatch is very small.[4] Sound practice of computerized probabilistic record linkage methodology has been well established in Canada,[5] beginning with the early work of Newcombe and his associates in the 1950s.[6] A variety of computer software has been developed for this purpose, such as Statistics Canada's Generalized Record Linkage System (GRLS).[7]

Record Linkage as a Tool for Health Studies

The methodology of record linkage has been used for a variety of medical purposes — to combine records relevant to patient care, to compile vital statistics and demographics, for epidemiological and genetic studies, and as a public health service (i.e., registries).[8] Epidemiological research designs, such as case-control studies and cohort analyses, both prospective and retrospective, can be used with linked files. Much of the Canadian literature focusses on the potential of record linkage for epidemiological follow-up, the study of short- and long-term effects of exposure to risk factors, or delayed harm which may result from those exposures. As

summarized by Smith,[9] the files to be linked can have various roles in a medical follow-up. A file could be:

- a starting point, which identifies the exposed (and unexposed) population;
- an end point, which identifies the outcome, i.e., death or the onset of disease;
- an intermediate file, which facilitates the linkage;
- a source of additional detailed information; or
- a tool to examine the reliability and accuracy of the methodology.

The various types of analysis possible through record linkage and the roles played by the files may best be illustrated with a hypothetical example (see Exhibit 1). Suppose that a researcher has noted an increase in the incidence of a congenital anomaly, such as limb reduction. This may be related to the use of a new prescription drug by the mother during pregnancy, for example, Thalidomide. A cohort study could be done in which the researcher would begin with women in a drug data base who did and did not use thalidomide (an exposure — the starting point). This would be followed up by linking to the vital statistics birth file and stillbirth files, which would indicate any births to these women and give the children's identifying information (an intermediate file). Finally, this combined file could be linked to children in a congenital anomalies registry, noting those with limb reduction (the outcome — the end point).

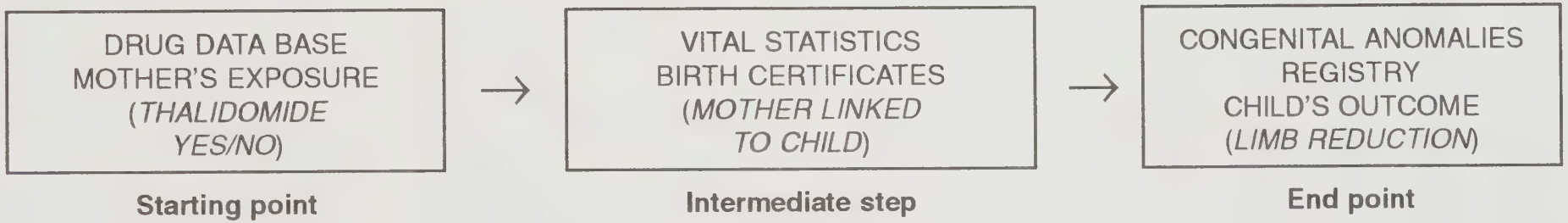
Alternatively, if a number of drugs are suspected, a case-control study could be set up. The starting point for this research design would be the outcome. A congenital anomalies registry could be used to provide a list of children with limb reduction (the starting point). These cases could then be linked to a vital statistics birth file to provide the mother's identifying information and to obtain a control group of children born in the same time period who did not have limb reduction (were not registered). This intermediate file could then be linked to a data base that notes the mother's use of prescription drugs to see if the use of any are associated with limb reduction (the end point).

To summarize, record linkage can provide data for analyses of possible relationship(s) — in this hypothetical example, between thalidomide and limb reduction — using existing information, without putting further pregnancies at risk.

The use of record linkage can facilitate research designs to study reproductive technologies and the outcome for the child. However, it should be noted that record linkage studies may not provide complete answers in themselves. They do, however, aid the investigation of whether a particular hypothesis is likely, and they can lead to a refined hypothesis that could dictate more specific research designs such as randomized controlled trials. Like all research methodologies, it has advantages and disadvantages, and/or concerns associated with it.

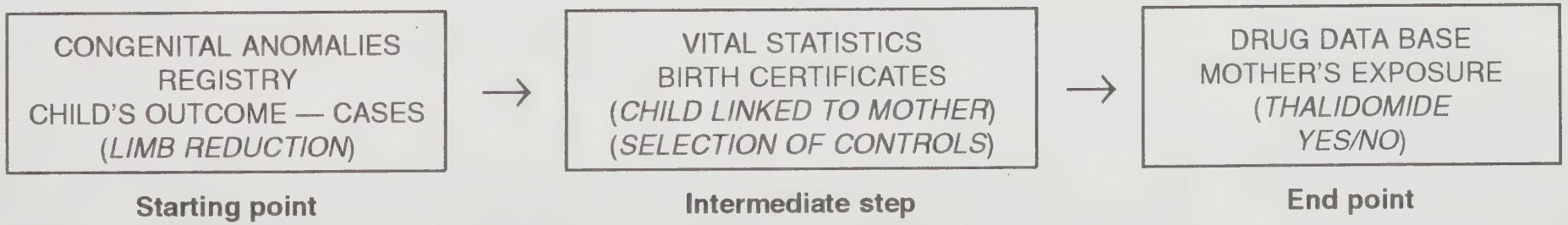
Exhibit 1. Possible Roles of Data Bases Being Linked for Standard Epidemiological Research Designs — An Example

Cohort Study



Starting point **Intermediate step** **End point**

Case-Control Study



Starting point **Intermediate step** **End point**

Advantages of Record Linkage for Research

The advantages of record linkage as described in the literature are numerous.[10] Many advantages are particularly relevant when studying reproductive outcomes. For example:

- The costs associated with linking to existing files are usually less than those of conducting a comparable survey, since data collection and entry have already been done and the system "debugged."
- At little extra cost the total population, rather than a sample, can be studied, which ensures the inclusion of rare events.
- The use of total population also minimizes selection bias, notably providing large unbiased comparison group or groups.
- There are fewer losses to follow-up due to moving, etc., with the probabilistic matching of large population files.
- The response burden can be greatly reduced, particularly when dealing with sensitive topics, such as infertility or the loss of a baby.
- By combining an outcome file with an exposure file, it is possible to examine relative risk in addition to the prevalence statistics provided by the component files.
- The data is collected prospectively, is less subject to faulty recall, etc.
- Record linkage may provide the only source of information available at present.

Disadvantages of Record Linkage

There are also concerns about or disadvantages to the use of record linkage methodology that should be noted:

- There are confidentiality issues and ethical concerns associated with the use of administrative data for purposes other than those for which they were collected, and real or perceived invasion of privacy when dealing with sensitive information or matters such as health.
- There are jurisdictional concerns, the resolution of which may require much negotiation if the data sets to be linked are not owned by the same agency or controlled by the same legislation.
- Communication problems can occur if the data bases are not at the same location.
- There are constraints on how variables are collected and coded. The researcher is limited to what is recorded.

- The time required in preprocessing to create compatible data sets can be costly.
- Linkages using data sets based on samples, such as surveys, may not be able to capture rare events.
- Studies based on record linkage are retrospective, examining past events.
- There can be a time lag in the availability of administrative files.
- Although bias checks can be made for non-links, the possibility of error due to false links remains.
- The researcher may suffer from data overload (i.e., there may be too many directions to follow).

There is a need for appropriate protection and for policies to be developed to manage harms from exposures to risk factors. Because of concerns about the potential health effects of occupational, environmental, drug, and treatment exposures, confidentiality is an issue that needs to be weighed against the public's right to know. Access to many data bases is already controlled by legislation such as the Privacy Act and the Statistics Act, and great care is taken to ensure that only statistical tables — and no personal information — is released. Yet, as the Task Force on Health Information has noted, "even when full safeguards are in place, there is the risk of public perception of invasion of privacy with subsequent resistance to provision of data, in practice or via policy."[11] However, the Task Force also notes that health research is more easily recognized as "public good" than are other scientific disciplines. Carefully controlled record linkage could be acceptable, if the product was perceived to be in the public interest.

Specific Issues Associated with the Study of Reproductive Technologies

When examining the potential of record linkage for the study of reproduction, there are also some specific issues that should be addressed:

- the "newness" of the technologies and the general lack of information;
- public sensitivity to the topic;
- cross-generational analyses; and
- possible introduction of bias relevant to the field of study.

Each of these issues is discussed briefly below.

"Newness" of the Technologies

As mentioned in the introduction, due to the relative newness of many of the technologies, little is known about their short- and long-term outcomes. In addition, only a small portion of the population has used

them and the exposure and/or the outcome are relatively rare events. While record linkage can be timely in that it allows use of existing information, enough time may not have elapsed for outcomes to appear in administrative data bases. If alternative sources of data are available, an analysis of these may be more timely. In addition, it is important to examine whether such rare events can be captured economically using record linkage.

The usefulness of record linkage will largely depend on the analysis being done. In many cases there may be few relevant sources of data. If there is sufficient information in existing data files, record linkage could be a productive method to use in the analysis of rare events. For example, if one wished to study the outcomes of a particular fertility drug, the starting point would be the rare event — those women in a data base who have used the drug. This subfile of users could then be linked with an outcome file that included the total population (e.g., vital statistics such as birth records) to create a cohort study that would involve little loss in follow-up. If, on the other hand, the researcher linked the user subfile to a sample survey as an outcome file, the odds that the women were also surveyed would be small, and many cases could be lost in follow-up. In the latter case, record linkage would not be productive. In assessing the utility of record linkage, the researcher should take into consideration how rare the event may be and choose a research design that will maximize returns.

A Sensitive Topic

Of all the health topics that could be studied, reproduction is perhaps the most sensitive and private. This may explain why many of the gaps in information identified by the Task Force on Health Information are related to reproduction. The private nature of the topic makes confidentiality especially important. People may be reluctant to answer questions concerning reproduction and infertility, and great care must be taken to ensure confidentiality.

Response burden also becomes an important consideration when dealing with this sensitive topic. Because many reproductive studies involve relatively rare events, if new data were to be collected for every study, eligible respondents could be approached repeatedly. It stands to reason that there is a limited number of times a mother should be expected to discuss a sensitive topic — for example, a painful experience such as the loss of a baby. The advantage of secondary analysis of existing data using record linkage is that it can avoid repeated interviews with the same subject.

Cross-Generational Analysis

The very nature of the study of reproduction involves two generations, the parents and the child. Risk factors experienced by the parents could have child health outcomes. This means that records concerning the mother's exposure to those risks would have to be linked to records concerning the child's health. Often this necessitates the use of an

intermediate file, or possibly two, further complicating the record linkage process. For example, a researcher may be examining the relationship of the mother's exposure to radiation with the child's development of cancer. The exposure data base, possibly a dose registry, would concern the mother only, while an outcome data base, such as a cancer registry, could contain information on the child only. To link these two files, it would be necessary to find a data set, such as birth records, that would contain identifying information on both the mother and the child. This would act as an intermediate file. Yet, the dose registry may contain information on the exposure of the mother before and/or after she married. It may be necessary to use a second intermediate file — marriage records — to clarify the mother's married and/or maiden name before linking to the birth records. In sum, the researcher should be aware that cross-generational analysis of reproductive outcomes often requires more than one linkage.

Possible Introduction of Bias

Retrospective cohort studies, and case-control studies are very sensitive to bias in the selection of cases and controls.[12] When linking records it is important that the researcher assess the possibility of bias in the records that are linked compared with those that are not. For example, the Commission heard from a number of presenters at the public meetings who were concerned with issues associated with immigrant or "ethnic" women, such as pressure to become surrogate mothers, or to abort fetuses because of a cultural preference for one sex, or their lack of resources to support a disabled child.[13] Record linkage software often first links on the basis of sex, name, and date of birth. Sex and date of birth are usually well reported,[14] but names present a greater challenge. These may be incorrectly entered, spelled in a variety of ways, or shortened. Some ethnic groups may have many last names, and the order in which they are used may vary. Programs have been written, such as Statistics Canada's NAMECHECK,[15] to compare names with a dictionary of common names to help identify possible problems and to generate alternative names, such as Peggy for Margaret. However, many non-English names may not be in the dictionary and may be difficult to verify. In addition, short two- or three-letter names are used by a high proportion of Asians and may not have enough discriminating power.[16] The loss of potential links due to name problems could introduce an important bias into an analysis of changing sex ratios, for example. Thus, the researcher should check for the presence of biases that could be relevant to their thesis and try to minimize them (the possible bias in the above example can be minimized by attempting a second pass of the non-linked data, matching primarily on a different combination of the identifying variables).

Descriptors Used for Data Base Assessment

To address both minimum outcome-related criteria and additional record linkage criteria for the assessment of record linkage potential, three

general descriptor areas must be examined. These are general data base characteristics, technical characteristics, and ownership and access. The rationale for each of these areas is described briefly below.

General Characteristics

The first area of interest concerns a general description of the data base, its purpose and design, target population, population coverage, data collection, time period, and size. General characteristics of the data base, such as the overlap of target populations and time periods, can be important in assessing link potential for a number of reasons. If there is little overlap with respect to these two characteristics between two or more data bases, few linked records will likely be generated. In instances where there is little overlap in target populations of exposure and outcome data bases, record linkage would contribute little.

Linkages will also be restricted by poor population coverage. For example, if it is estimated that only one individual in a thousand is included in the data base, the number of links will be limited and information on relatively rare occurrences would be lost. This issue will be important in the examination of outcomes of new reproductive technologies, since a very small percentage of women are exposed to these interventions and treatments. In addition, coverage can greatly influence the roles a data base may play in the linkage. Data bases with poor population coverage are generally only suitable as starting points. For these reasons, a relatively large number of questions are asked to assess population coverage.

The size of the data base in terms of total number of records is significant in assessing linkage possibilities. The linkage of small data bases may not produce a sufficient number of links or cases on which to base an analysis. Large data bases, however, require more computer time and can be more costly to link. In general, large ongoing data bases with good coverage have large linkage potential. If the coverage is poor, the linkage of large data bases may not be any more productive than the linkage of small ones with good coverage of the target population, but could be considerably more costly.

Finally, whenever coverage is an issue, it is important to identify known biases with respect to subgroups of the population or sample. Biases that are common in survey research, such as an over-representation of more highly educated respondents, should be identified, if possible, and examined to assess how they might affect outcome conclusions.

Each of these general characteristics could eliminate data bases from further consideration. If there is little common ground, technical concerns with data linkage would be academic.

Technical Characteristics

Data bases' technical characteristics are critical to the linkage of relevant data. It is thus important to consider the storage of data, the unit of analysis, the presence of identifying variables, the sort sequence, and

whether the data base has been linked with other data sets. These characteristics can greatly influence the potential for linkage and the amount of preprocessing and reformatting required.

The presence of identifying variables at the appropriate level (usually individuals) is of primary importance. Some key identification variables used by Statistics Canada are surname, other ever-used surnames, given names, sex, date of birth, province or country of birth, and social insurance number (SIN).[17] Data bases with common identifiers are easily linked. Those with large numbers of identifiers can also function as intermediate files. If the data bases of primary interest have different identifying variables, it is sometimes possible to link through an intermediate data base that has identifiers common to each of the data sets. For example, birth certificates contain parental identifiers and child identifiers, and thus have been used to link data sets containing only the mother's name to child-related data bases. For this reason, it is important to question for the presence of a large number of potential identifiers, as is done at Statistics Canada.

The storage of the data base is important because it influences cost-related factors such as the amount of preprocessing and reformatting required. Data bases that are not in machine-readable form may have a prohibitive cost for record keying. In some instances, outcome data may be in a machine-readable format, while the identifying variables needed for record linkage are not. Whether the data base is software-defined can also be worth noting. Translation programs have been written to make software-defined data bases compatible. However, this process can be tedious and time-consuming.

Furthermore, if the files to be linked have different units of analysis, it also adds to preprocessing requirements and cost. For example, in a treatment-focussed data base, it is necessary to combine records of treatments given to individuals to create individual case histories before linking the data base to an individual outcome file.

Whether or not the identifying variables in a data base have been sorted sequentially is another small technicality that could affect the efficiency of record linkage. It may be more time-efficient and cost-effective to have large files stored in a presorted format, but it is only an advantage if the other data base to be linked can be sorted on comparable identifiers.

The previous record linkage history of the data base has implications for record linkage potential. Many of the preprocessing and reformatting processes may have already been done and procedures and policies for linkage developed. Previous linked data sets could also be useful as intermediate data bases. Thus, it is important to know which specific data bases have been previously linked.

These technical characteristics are important both practically and economically in the assessment of the feasibility of record linkage.

Ownership and Access Characteristics

Finally, issues concerning ownership of data and form of access are important. The ownership and location of data, requirements for access, and type of access and use permitted can be critical when trying to assess potential confidentiality, and jurisdictional and communication issues. Restrictions in these areas generally increase costs and the amount of technical support required.

Data Collection Methodology

The data collection process used in this project involved three steps:

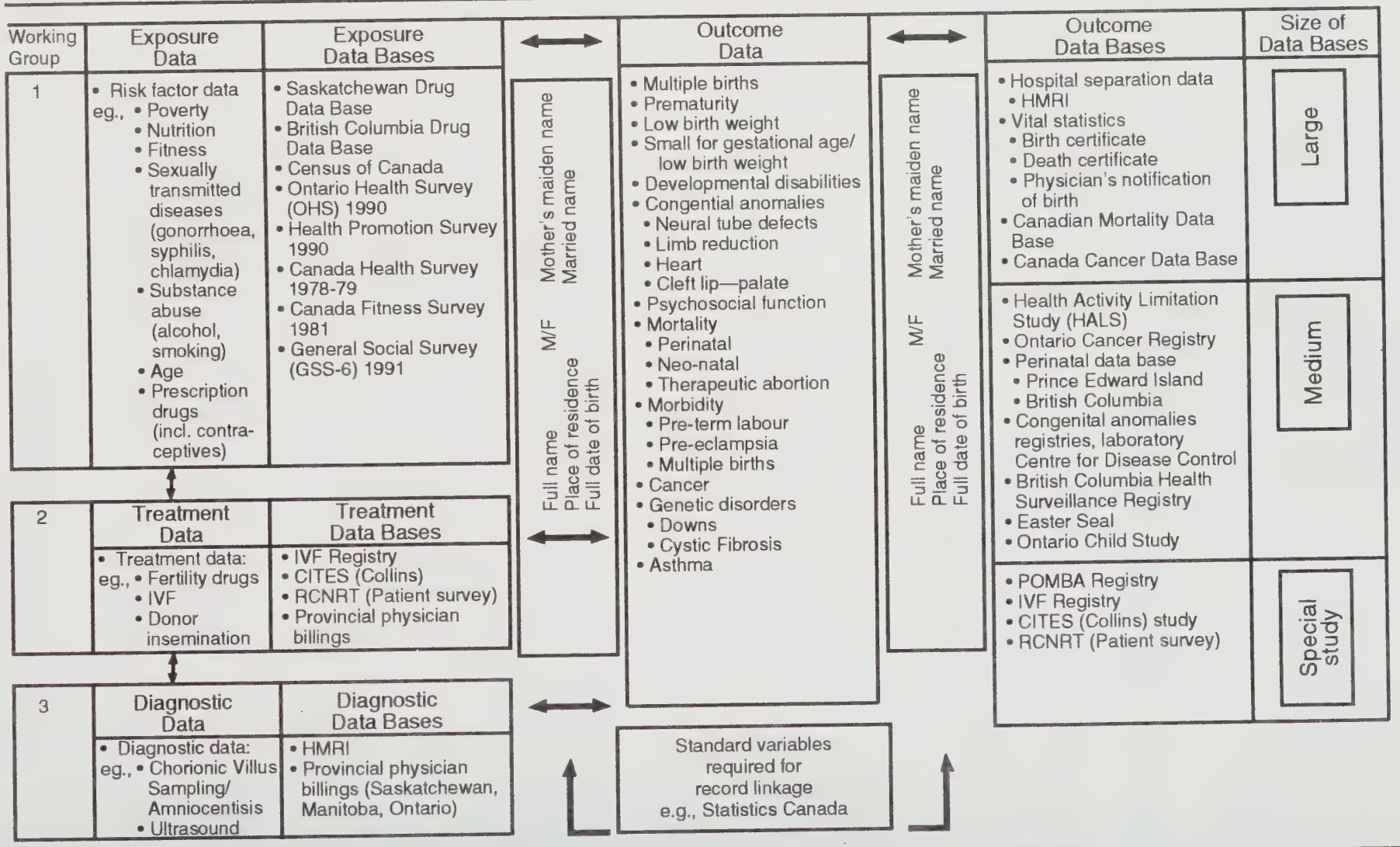
- selection of the data bases;
- development and distribution of the questionnaire; and
- verification of data base assessments and descriptions.

Selection of the Data Bases

During the formative stages of this project, the Commission developed a preliminary conceptual framework for the study of child health outcomes. The conceptual grid identified the risk factors, treatments, and diagnostics to be examined, child health outcomes of interest, and relevant data bases (Exhibit 2). Two separate studies were undertaken to investigate the feasibility of record linkage. This project examines data bases with a number of risk factors, including poverty, nutrition, fitness, substance abuse, age, and prescription drug use, as well as fertility treatment and diagnostic procedures, and assesses the feasibility of linking to data bases containing child health outcomes. A second study examines the feasibility of linking occupational and environmental exposure data bases to reproductive health, including child health outcome.[18] The list of data bases outlined in Exhibit 2 (approximately 20) formed the first wave of data bases to be queried. In turn, the guardians of these data bases suggested other data bases that could be of interest — the second wave. In total, over 40 data bases were examined. Given the time constraints, this could not be an exhaustive list; however, many relevant data bases have been included. The data bases considered for inclusion in the catalogue fall into several major groupings covering infertility risk factors, treatment, and outcome. The groupings are:

- national integrated data bases, such as the Canadian Mortality Data Base;
- national cross-sectional population sample surveys, such as the Canada Health Survey, 1978-79, and the Canada Fitness Survey, 1981 and Follow-Up;

Exhibit 2. Revised Conceptual Grid: Child Health Outcomes and AHR



- national specialized data bases or registries, such as the Canadian Congenital Anomalies Surveillance System or the IVF Registry;
- provincial population-based data bases, such as the Ontario Health Insurance Plan (OHIP) Claims File and other provincial equivalents;
- provincial cross-sectional sample surveys, such as the Ontario Health Survey, 1978-79, and the Quebec Health Survey (Enquête Santé Québec); and
- provincial specialized data bases or registries, such as the Nova Scotia Perinatal Data Base or the British Columbia Health Surveillance Registry.

A complete list of data bases explored for feasibility of record linkage is contained in Appendix 1.

Development and Distribution of the Questionnaire

A self-administered questionnaire to be completed by data base guardians (Appendix 2) was developed, incorporating the descriptors identified as important to the assessment of record linkage potential discussed earlier. This questionnaire was pretested with four data base guardians, modified, and approved by the Commission before distribution.

Prior to sending the questionnaire, identified guardians were contacted by telephone to briefly introduce the study and the research team, and to inform them of the purpose of the data collection, and the time frame. At that time the name of the guardian's data base, and whether the guardian had more than one data base relevant to this project was determined. Finally, the name of the contact person for the questionnaire, the mailing address, and telephone and fax numbers were confirmed.

A covering letter was sent with each questionnaire. The letter included a brief description of the study's purpose, process, and time frame. If the data base guardians had questions, a contact name and telephone number from the Commission (for questions about the study's purpose) and a contact name and telephone number from the consulting team (for questions about filling out the questionnaire) were provided. In addition, a request was made for data base-related materials and documents, such as questionnaires and coding manuals. Finally, they were asked for names of other researchers doing similar work relevant to the Commission.

Follow-up telephone contacts were made with 50 percent of the guardians to clarify responses provided by respondents, and to help fill in any missing information.

The response to the questionnaire was excellent, especially given the tight time frame, with all of the data base guardians responding.

Verification of Data Base Assessments and Descriptions

Once the questionnaires were returned, the record linkage potential of each data base was assessed using the criteria described below. To verify this assessment and to discuss other relevant issues associated with record linkage, representatives of record linkage centres across the country, many of whom were data base guardians, were invited to a day-long meeting. In advance of the meeting participants were sent a draft of the section of this report entitled "Assessment of Record Linkage Potential" and a proposed agenda.

The meeting had four specific objectives: to discuss and reach agreement on the record linkage potential of the selected data bases to be included in the catalogue; to confirm the catalogue layout; to reach agreement about general feasibility issues with respect to record linkage in the area of new reproductive technologies; and, finally, to put forth some practical suggestions to help facilitate research in this direction.

There was general agreement among participants at the meeting on the assessment of record linkage potential for each of the selected data bases. The proposed catalogue format was also well received. It was recommended that the guardians for each selected data base be sent a proof of their catalogue page for final inspection prior to submission of the catalogue to the Commission. This was acted upon by the consultants.

In addition, the participants made a number of helpful comments related to research using the record linkage approach. First, it was agreed that a catalogue of existing data bases would be a very useful tool for researchers, particularly those starting out in their endeavours. Then, several suggestions were made with respect to specific methodological issues, such as the lack of standardization in the way variables are collected and coded. Participants also spoke of the need for a national strategy that would lead to more interprovincial cooperation and the development of central data bases. Some participants felt that the benefits of record linkage were not widely known or appreciated.

Assessment of Record Linkage Potential

Relatively early in Canada's use of record linkage for health research, it was recognized that

> A clear distinction must be made between the linkages that are most likely to be immediately profitable and others which will become worthwhile in due course ... In attempting to single out the former, some priority should be given to records that are already centralized in machine readable form and could be made linkable without much difficulty.[19]

For similar reasons, the present assessment of the record linkage potential for the analysis of child health outcomes divides the data bases into four groups: those with high record linkage potential, good potential, possible potential, and poor potential — using the criteria discussed below.

Criteria for the Assessment of Record Linkage Potential

The criteria used to place the data bases in each of these four groups generally deal with the following:

- content (basis for initial selection, as discussed above);[20]
- coverage of the population;
- size of the data base;
- presence of sufficient personal identifiers; and
- access to the data base with respect to record linkage.

These criteria are used in combination to assess the record linkage potential of the data bases. It is important to consider all of them since each has an effect. Some of these criteria are more critical in the placement of the data bases than others and are briefly discussed below.

Coverage of the Population

The coverage of the population can be important in assessing data base potential because it defines the role a file can play in record linkage (i.e., as a starting point, an intermediate file, or an end point). If coverage is high, say 95 percent or better, the file can be used in all three roles. The researcher could expect little loss in follow-up and little selection bias. This could also be the case for files with moderately high coverage, say 85 percent, if possible bias is known, and the researcher has determined that the bias will not affect the analysis. Hence data bases with high coverage have more flexibility in their use and could be used in a number of different analyses.

In contrast, data bases with low coverage are largely limited to the role of starting points, and care must be taken to assess possible selection bias. Sample surveys are prime examples of such files. Even large national surveys rarely interview more than 1 percent of the eligible population. Few are based on simple random samples. They usually need to be weighted in order to represent the population appropriately.

Because the provinces' health care systems differ, geographical coverage should also be considered. If possible, it is desirable to have national coverage so that possible regional differences can be assessed.

For the reasons noted above, data bases with high coverage are considered to have a high record linkage potential. However, coverage alone is not sufficient to determine the placement of a data base in the four groups of record linkage potential.

Data Base Size

A very general definition of data base size is used in this assessment. It includes the unit of analysis, time period included in the data base, and number of records. Although not of prime importance, size should be taken into consideration. The number of cases available after linkage can greatly influence the type and level of analyses that can be conducted. For example, large multivariate analyses that take into consideration the complexity of health issues are not possible with small case bases.

The unit of analysis must be considered for a variety of reasons. Record linkage is usually done at the individual level. A data base with events (such as doctor visits) as the unit of analysis may appear to be large. However, after the events have been combined to form individual case histories, the data base will be much reduced in size. In addition to the size issue, it should be noted that data bases with a unit of analysis that is not at the individual level can require considerable preprocessing and, consequently, higher costs.

The time period a data base covers is noted to assess possible overlap between the data bases one may wish to link. It also influences the size of the case base that can be used for analysis.

Size was one of the less important criteria in this assessment. Generally, it was used to identify data bases that may not have large enough case bases after linkage to support analysis.

Presence of Personal Identifiers

The presence of personal identifiers is crucial to the assessment of data base record linkage potential. A minimum of five personal identifiers — surname, given names, sex, detailed birth date, and country or province of birth — are required to reduce linkage ambiguity.[21] Data bases were deemed to have good personal identifiers if they included the minimum identifiers. In the absence of all or some of these identifiers, data bases were assessed as having fair identifiers if they had a relatively large number of other identifying variables or an identifying number, such as the health insurance number. (The health insurance number may make it possible to link to an intermediate file that could supplement the number with the missing identifying variables.) Data bases with few personal identifiers were classified as poor. In some cases, identifiers may have been available, but not in machine-readable form, or from another source, such as another data base, or possibly through a third party who provided the sample or who was contracted to do the data collection. In these instances, the data base guardians know who to contact for the information but not necessarily the quality of the identifiers or whether they are in machine-readable form. Such identifiers were noted, but to be useable they could require much preprocessing.

Access to the Data Base for Record Linkage

The record linkage history of data bases can also be important in the assessment of record linkage potential. If a data base has been linked to other data bases, it is likely that preprocessing concerns have already been addressed, that policy and procedures have been developed regarding record linkage requests, and that resources would be available for record linkage. In most cases, these data bases would be the most immediately linkable. However it should be noted that there may be some relatively new data bases that do not have a history of record linkage, but have been created with data linkage in mind, and would meet many of the access criteria noted above.

Data Bases with High Record Linkage Potential

Data bases with high record linkage potential can be seen in Exhibit 3, which summarizes how they fulfil each of the record linkage criteria: coverage of the population, size of the data base, presence of identifying variables, and access for record linkage. The content of the data bases is also briefly summarized, to help assess the utility of the record linkage in terms of the types of studies that would be possible. More detailed descriptions of these data bases, arranged in alphabetical order, can be found below.

In general, the data bases in this group have high coverage of the target population, usually 95 percent or better. Some are national. The unit of analysis is generally at the individual level and the files are large. They all include the minimum personal identifiers, and most have a history of record linkage, established policies, and the resources required for record linkage.

Concerning the exceptions (i.e., the data bases with less coverage) the Manitoba Permanent Medical Statistical File (85 percent coverage) has known biases that can be examined. The British Columbia Health Surveillance Registry has a number of ascertainment sources, is considered to be comprehensive, and coverage is estimated to be high (85 percent or better); however, the exact proportion of the target population included is unknown.

In addition, although the provincial data bases, considered alone, do not allow for an examination of the possible effect of the different health care systems, in some cases they can be combined for this purpose — for example, hospital separation data bases and cancer registries. In other cases, the provincial data bases provide a good source of important information, such as the Out-Patient Prescription Drug Data File in the Saskatchewan Health Data Bases. In addition, it should be noted that the Quebec data bases that have been included in this group have high technical potential for record linkage. Researchers wishing to link these data, however, should be aware of the highly sensitive nature of record linkage issues in this province.

Exhibit 3. Data Bases With High Record-Linkage Potential

| | Assessment criteria | | |

Also included are two data bases currently being developed that will have high record linkage potential: the Prince Edward Island Perinatal Data Base and, particularly, the Canadian Birth Data Base. The Canadian Birth Data Base is currently in the pilot stage at Statistics Canada and will have a similar format to the Canadian Mortality Data Base (i.e., it is being set up specifically for record linkage). This will be particularly useful in the study of risk factors and reproductive outcomes, since birth files are normally used as intermediate files which link the mother and child, and can also be a starting point or end point. Few studies of reproductive outcome would not use birth records. In addition, the repeated use of a large preprocessed data base is very cost-effective.

In general, these high potential files have a great deal of flexibility in terms of the roles they can play. Because of their high coverage, they could be starting points, intermediate files, or end points. However, many of them contain only outcome information. This will place some limitations on the research areas that can be pursued using data bases with high linkage potential only. However, within these limitations, there are important studies which can be done. For example, a major information gap noted by the Task Force on Health Information regarding the short- and long-term effects of low birthweight on the child's health[22] can be addressed by linking outcome data bases.

The data bases in the high record linkage potential group that contain exposure and/or treatment information are provincially based. As starting points, these data bases can be linked to national data bases with the understanding that the findings may only represent the situation in specific provinces and not the national situation. The inclusion of data bases in the second group, those with good record linkage, may improve this situation.

Data Bases with Good Record Linkage Potential

The data bases classified as having good record linkage potential have been summarized in Exhibit 4. The main criterion distinguishing this group from those with high potential is coverage. These data bases are surveys that sample less than 1 percent of the target population. For this reason they can only be used productively as a starting point in a record linkage. They have been identified as having good record linkage potential because, within these limitations, they have good personal identifiers and, usually, a record linkage history. They are based on scientific sampling frames, usually with known biases, allowing the researcher to estimate the effect of such bias. However, rare events may not be captured in linked data sets using these data bases. In addition, the target population for most of these surveys is the general adult population. Once women of childbearing age are extracted from these data bases and linked to outcome data bases, the sample size is considerably reduced. Considering these restrictions, the size of the data base can be important, and only those with more than 20 000 cases have been included. Whether this limit ensures a large enough case base will have to be examined by each potential

Exhibit 4. Data Bases With Good Record-Linkage Potential

	Assessment criteria																							
	Content				Coverage				Size				Identifiers				Access							
																				Resources available		
	Exposure	Treatment	Diagnosis	Outcome	Geographical area	Sample	Known bias	Coverage %	Individual level	Time period	Number of records	Total or (per year)	Good	Fair	Poor	Other source	Previous linkage	Established policy	Indirect access only	Software	Machine time	Personnel
Canada Health Survey (CHS) 1978/79	●				Can.	●	●	<1	●	1978-79	31 668		●				●	●	●	●	●	●
Canada Fitness Survey 1981 and Follow-up 1988	●				Can.	●		<1	●	1981	23 400		●				●					
Ontario Health Survey (OHS) 1990	●	●			Ont.	●	●	<1	●	1990	61 239		●					●	●	●	●	●

researcher, given the relationships to be examined and the type of analysis required. Recognizing these limitations, these data bases, in combination with the data bases with high record linkage potential, can provide information concerning many of the research areas of interest to the Commission, especially those relating to exposure to such risk factors as poverty, fitness, substance abuse, and age.

Data Bases with Possible Record Linkage Potential

A more diverse set of data bases is found in the third group, those with possible record linkage potential (Exhibit 5). In general, these data bases are classified by their lack of good personal identifiers. In many instances, these data bases include health insurance numbers and have been classified as having fair identifiers. If intermediate files can be found that supplement the health insurance number with the minimum personal identifiers, these data bases could have high or good record linkage potential. Data bases with poor personal identifiers (e.g., Ontario Child Health Study (1983) and Follow-Up, 1987; Quebec Health Survey (Enquête Santé Québec), 1987 have also been placed in this group, because there may be alternative sources of personal identifiers available in machine-readable form that could be used to supplement the identifiers.

The one data base with good identifiers placed in this group is the General Social Survey. This survey of the Canadian adult population, with only about 12 000 respondents, is relatively small and may not provide enough cases for analysis after linkage. It has been included in this group because it has high technical potential for linkage in terms of identifying variables and linkage history. It could also have good overall linkage potential if it is found to have a sufficient case base for specific research designs.

Data Bases with Poor Record Linkage Potential

For a variety of reasons some data bases have been classified as having poor record linkage potential (Exhibit 6).

The Canadian Infertility Therapy Evaluation Study (CITES) has been included in this list because it lacks good identifying variables in a centralized, machine-readable form. At present, personal identifiers are only available at participating clinics, some of which may not have retained this information after completion of the study.

The data bases collected by the Parents of Multiple Births Association of Canada Inc. (POMBA) have similar problems. At present, these data bases are not in a centralized, machine-readable form, and the association currently has few resources to correct this. The estimated coverage of the eligible population is fairly small (10 to 20 percent) and is biased in favour of those with successful outcomes who have sought a support group, such as POMBA's local member groups. However, the data collected by this association are rich in variables that are of interest to the study of reproductive outcomes associated with multiple births, and could be useful

Exhibit 5. Data Bases With Possible Record-Linkage Potential

| | Assessment criteria | | |

Exhibit 6. Data Bases With Poor Record-Linkage Potential

	Assessment criteria																							
	Content				Coverage			Size				Identifiers				Access			Resources available		
	Exposure	Treatment	Diagnosis	Outcome	Geographical area	Sample	Known bias	Coverage %	Individual level	Time period	Number of records	Total or (per year)	Good	Fair	Poor	Other source	Previous linkage	Established policy	Indirect access only	Software	Machine time	Personnel
Canadian Infertility Therapy Evaluation Study (CITES)	●	●			Can.	●		?		1988&91	2	198			●				●	●	●	●
POMBA — Triplet/Quadruplet/Quintuplet Registry	o	o	o	●	Can..			20		1985+		173				●						
POMBA — Impact of Multiples on the Family Survey	●	●	●	●	Can.			10		1992		1 169				●						
Easter Seal Client Registry				●	Ont.			?	●	"1992"		8 000	●						●			

o Will be collected in the future.

as pilot studies in this area. As things stand, however, these data bases have poor record linkage potential.

The Quebec Health Survey (Enquête Santé Québec), 1987 has been included in the list with poor record linkage largely because identifying variables are only available for the approximately 20 percent of respondents who voluntarily gave their names because they were interested in receiving further information concerning health programs. There is every reason to believe there is a selection bias in this subgroup, and much research would be required to determine the nature of the bias and its possible relevance to the study of reproductive outcomes. In addition, once linked, there may not be a large enough case base for analysis.

Finally, the Easter Seal Client Registry has been added primarily because of its coverage and the way in which the data are presently stored. This is a voluntary registry and the coverage of the population, with any associated biases, is unknown. In addition, only children with muscular-skeletal conditions that produce a physical handicap are eligible, which is a fairly restrictive outcome. The data bases are stored in the form of active client lists which are compiled each year. Hence, there is a large overlap from year to year, and the new computer system only dates from 1990. To use this data base for record linkage would require much preprocessing and research to assess population coverage and possible biases.

Other Data Bases Considered

Early in the data collection process, a few data bases were dropped from the list of data bases included in this catalogue because good identifying variables were not available in any form. Without good identifying variables record linkage is not possible. Among those dropped were the Royal Commission on New Reproductive Technologies (RCNRT) patient survey; Census of Canada; the Health and Activity Limitation Survey; Canada's Health Promotion Survey 1990; and the Ontario Reportable Diseases Information System.

In addition, the Manitoba Sexually Transmitted Diseases Data Base was omitted, despite the availability of good identifying variables, as legislation forbids record linkage for reasons of confidentiality.

Summary of the Record Linkage Potential

In summary, the data bases assessed to have high or good potential for record linkage present the best and most immediately profitable sources for linked studies investigating maternal and paternal infertility risk factors, infertility treatments and diagnostic procedures, and data bases pertaining to the child's health. The new Canadian Birth Data Base has perhaps the highest potential to further research in this area, and priority should be given to its development.

Only limited information is available in the data files assessed to have high or good linkage potential on fertility treatments, such as the use of fertility drugs in Saskatchewan. At best, files with detailed information on fertility treatments, such as the IVF Registry, have been classified as having possible record linkage potential because of the absence of key identifiers.

Statistics Canada has developed 'Standard Data Collection Package for Medical Follow-Up Studies'[23] to help standardize the collection of health information so that it can be linked to outcome files. As part of this package, they have developed software to create a data base that facilitates linkage. By using such a system, it is hoped that some of the problems faced when attempting data linkage can be minimized. These include: insufficient identifiers, non-retention of records, costs of recovering lost information, incomparability of information, and event rather than individual record keeping. Any researcher, corporation, or group interested in a health follow-up of individuals would be well advised to look at this package before collecting data. Even if they choose to use their own software, the costs of data linkage could be greatly reduced by collecting the standard information outlined in the description of this package. If confidentiality is an issue, such a data collection system could be used not for release, but for their internal filing system. It would, therefore, retain the necessary information should policy change and/or consent to use the information be given by the patients at a later date.

This assessment has focussed mainly on the technical feasibility of record linkage. Confidentiality and jurisdictional issues remain to be addressed. Many studies could be done using data bases under Statistics Canada's jurisdiction that are governed by the same record linkage policy and Statistics Act. Much will depend on the specific study, the data required, and the agencies involved; each case will have to be resolved on an ad hoc basis.

Record linkage as a research method is promising. Its use can significantly further knowledge of the relationships of parental exposure to infertility risk factors, some fertility treatments, and diagnostics with child health outcomes, in a timely and economic way. Therefore, provided that the research conditions are carefully controlled and the confidentiality of the individuals being studied is safeguarded, this methodology should be pursued.

Record Linkage Potential Cross-Reference Charts

To facilitate quick reference to data bases in each record linkage potential group, this section contains cross-reference charts (Exhibits 7 to 10) based on a modified version of the exhibits from the previous section. The charts summarize how the data bases fulfil each criterion for record linkage: coverage of the population, size of the data base, presence of identifying variables, and access for record linkage. The characteristics of

each data base are also briefly summarized to help assess the utility of the record linkage in terms of the types of studies that would be possible. In addition, page numbers are given for the more detailed descriptions of these data bases. The detailed descriptions, catalogued in alphabetical order, are found below.

Exhibit 7. Data Bases With High Record-Linkage Potential: Cross Reference Chart

	Summary Description Page	Assessment criteria																							
		Content				Coverage			Size				Identifiers				Access				Resources available		
		Exposure	Treatment	Diagnosis	Outcome	Geographical area	Sample	Known bias	Coverage %	Individual level	Time period	Number of records	Total or (per year)	Good	Fair	Poor	Other source	Previous linkage	Established policy	Indirect access only	Software	Machine time	Personnel
British Columbia Cancer Registry	660				●	B.C.			90	●	1970+		(20 000)	●				●	●	●	●	●	●
British Columbia Health Surveillance Registry	663				●	B.C.			85	●	1952+		200 000	●				●	●	●	●	●	●
British Columbia Vital Statistics (VSTATS)	671				●	B.C.			100	●	1950+		3M	●				●	●	●	●	●	●
Canadian Birth Data Base (CBDB)*	680				●	Can.			100	●	1987+		1.1M	●					o	●	●	●	●
Canadian Cancer Data Base (CCDB)	683				●	Can.			100		1970+		1.2M	●				●	●	●	●	●	●
Canadian Mortality Data Base (CMDB)	690				●	Can.			100	●	1950+		6.25M	●				●	●	●	●	●	●
Quebec Cancer Registry	693				●	Que.			99		1982+		(25 000)	●				●	●		●	●	●
Manitoba Permanent Medical Statistical File	708		●		●	Man.		●	85		1969+		(13M)	●				●	●		●	●	●
Nova Scotia Perinatal Data Base	710				●	N.S.			100	●	1988+		(12 000)	●						●		●	●
OHIP Detailed Claims File	713		●	●	●	Ont.			100		1985+		(250M)	●				●	●	●	●	●	●
Ontario Cancer Registry (OCR)	715				●	Ont.			95		1964+		4M	●				●	●	●	●	●	●
Prince Edward Island Perinatal Data Base*	729	●	●		●	P.E.I.			100	●	1987+		(2 000)	●					o	o	o	o	o
Saskatchewan Cancer Registry	731				●	Sask.			100		1967+		4 073	●				●	●	●	●	●	●
Saskatchewan Health Data Bases	734	●	●	●	●	Sask.			94	●	1962+		>1M	●				●	●	●	●	●	●
Quebec Vital Statistics	737				●	Que.			99		1975+		(1.5M)	●					●		●	●	●

* Currently being developed, high future potential for record linkage.
o Will be developed in the future.

Exhibit 8. Data Bases With Good Record-Linkage Potential: Cross Reference Chart

| | Summary Description Page | Assessment criteria | | |

Exhibit 9. Data Bases With Possible Record-Linkage Potential: Cross Reference Chart

	Summary Description Page	Assessment criteria																						
		Content				Coverage				Size				Identifiers				Access				Resources available		
		Exposure	Treatment	Diagnosis	Outcome	Geographical area	Sample	Known bias	Coverage %	Individual level	Time period	Number of records	Total or (per year)	Good	Fair	Poor	Other source	Previous linkage	Established policy	Indirect access only		Software	Machine time	Personnel
British Columbia Linked Health Data Project	666		●	●	●	B.C.			100		1985+	(56M)			●			●	●	●		●	●	●
British Columbia Perinatal Data Base	669		●	●	●	B.C.			94		1986-89	(120 000)			●			●	●			●	●	●
Canadian Congenital Anomalies Surveillance System (CCASS)	686				●	Can.			79	●	1970+	174 516			●			●						
Quebec Health Survey	697	●				Qué.	●		<1	●	1987	(16 000)				●	●	●	●			●	●	●
General Social Survey (GSS-6) 1991	699	●				Can.	●	●	<1	●	1991	11 924		●				●	●	●		●	●	●
Hospital Medical Records Institute (HMRI)	701	●			●	Can.		●	80		1979+	(4.2M)			●			●	●				●	
In-Vitro Fertilization (IVF) Registry	704		●		●	Can.			100	●	1991+	(4 000)			●				●			●	●	●
Manitobia Chlamydia Data Base	706	●			●	Man.			85		1984-89	18 000			●			●	●	?		●	●	●
Ontario Child Health Study 1983 and Follow-up 1987	717				●	Ont.	●	●	<1	●	1983&87	(3 244)				●	●		●					

Exhibit 10. Data Bases With Poor Record-Linkage Potential: Cross Reference Chart

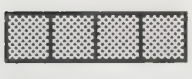
	Summary Description Page	Assessment criteria: Content — Exposure	Treatment	Diagnosis	Outcome	Coverage — Geographical area	Sample Known bias Coverage %	Size — Individual level	Time period	Number of records Total or (per year)	Identifiers — Good	Fair	Poor	Other source	Access — Previous linkage	Established policy	Indirect access only	Resources available — Software	Machine time	Personnel
Canadian Infertility Therapy Evaluation Study (CITES)	688	●	●			Can.	● ?		1988&91	2 198			●				●	●	●	●
Easter Seal Client Registry	695				●	Ont.	?	●	"1992"	8 000	●						●			
POMBA — Impact of Multiples on the Family Survey	723	●	●	●	●	Can.	10		1992	1 169				●						
POMBA — Triplet/Quadruplet/Quintuplet Registry	726	o	o	o	●	Can.	20		1985+	173				●						

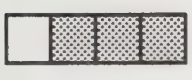
o Will be developed in the future.

Data Base Summary Descriptions

Summary descriptions of each data base are listed in this section in alphabetical order by data base name. These descriptions have been designed to give the user of this catalogue sufficient information to identify data bases that may be of interest, the address of the data base, and the name and telephone number of a contact person who can provide more detailed information.

To aid comparisons among data bases, a consistent format, which is fairly self-explanatory, has been selected for these descriptions. The name of the data base and its mailing address appear in the upper left-hand corner of the first page. Opposite this, in the upper right-hand corner, is a symbol indicating the record linkage potential of the data base for those who wish to browse through this section without referring to the cross-reference charts. The shaded portion of this symbol corresponds to linkage potential:

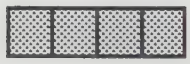

high potential


good record linkage potential


possible record linkage potential


poor record linkage potential

The body of the descriptions has been organized in point form under three major headings: general characteristics, technical characteristics, and access, with subheadings under each.



British Columbia Cancer Registry

British Columbia Cancer Agency
Division of Epidemiology
600 West 10th Avenue
Vancouver, British Columbia
V5Z 4E6

General Characteristics

Purpose	•	to provide a permanent record of all cancers diagnosed for B.C. residents, for use in etiologic and clinical research, and health care planning and evaluation
Relevant content	•	diagnoses of all neoplasms (ICD-9 codes 140-239), date of diagnosis, method of diagnosis, age at diagnosis, primary site, topography, morphology, etc.
Target population	•	B.C. resident population
Coverage	•	no known bias
	•	estimated proportion of the target population included is greater than 90%
Data collection	•	ongoing data collection process, continuously updated
Time period	•	data are available for 1970 to the present, with an unlimited retention period
Size	•	20 000 records per year, approximately 400 000 records in total
Unit of analysis	•	individual or event (cancer diagnosis)

Technical Characteristics

Data storage	•	in machine-readable form as a custom data base (UNIX)

Previous record linkage

- British Columbia Mortality Data Base and various cohort data bases (usually occupational groups)

Identifying variables (approximate percentage of records)

- surname (100%)
- alternate surname (20%)
- first given name (100%)
- first initial (100%)
- second given name (50%)
- second initial (90%)
- usual name or nickname (10%)
- sex (100%)
- marital status (50%)
- year, month, and day of birth (95%)
- birth province or country (40%)
- birth city or place (40%)
- mother's maiden name (10%)
- own place of residence, province or country (40%)
- postal code (95%)
- last known year alive (100%)
- year, month, and day of death (100% of deceased)
- place of death, province or country (100% of deceased)
- place of death, city (100% of deceased)
- social insurance number (10%)
- death registration number (100% of deceased)
- health insurance number (30%)

Access

Policy

- established policy and procedure

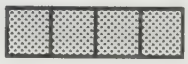
Procedure

- contact with the registry director, a written proposal which includes: purpose, nature of use, data required, format, confidentiality and security provisions

Type of access

- indirect

Resources available	• software (UNIX custom software), machine time, and experienced personnel
Costs	• quote prepared for each request
Contact person	• Dr. Mary McBride, Epidemiologist (604) 877-6000 ext. 3060



British Columbia Health Surveillance Registry

Division of Vital Statistics
Ministry of Health
818 Fort Street
Victoria, British Columbia
V8W 1H8

General Characteristics

Purpose	• to provide prevalence data on handicapping conditions among children, including congenital anomalies and genetic conditions
Relevant content	• name, parental/spouse name, address code, birth date, date of death, cause of death, diagnosis (ICD-9), date of onset of diagnosis, etiology code, etc.
Target population	• initially only B.C. children up to the age of 19 years with handicapping conditions; in recent years adults have been included
Coverage	• known bias — prior to 1964, information was not obtained from vital stillbirth and death records; also a voluntary registry with lower ascertainment for mild conditions
	• estimated proportion of the target population included (about 85%) is as complete as possible in recent years due to multiple ascertainment sources, resulting in high coverage for severe problems
Data collection	• ongoing data collection process, updated continuously
Time period	• data is available for 1952-1991, with an unlimited retention period
Size	• approximately 200 000 records in total
Unit of analysis	• individual

Technical Characteristics

Data storage
- in machine-readable form as raw data

Previous record linkage
- has been linked to physician's notice of birth, birth, stillbirth, and death registration records

Identifying variables (approximate percentage of records)

- surname (100%)
- first given name (100%)
- second given name (90%)
- sex (95%)
- year, month, and day of birth (95%)
- birth province or country (75%)
- father's surname (50%; higher % for children)
- father's first given name (50%)
- father's second given name (40%)
- mother's maiden name (65%; higher % for children)
- mother's first given name (65%)
- mother's second given name (40-50%)
- own place of residence, province (100%)
- own place of residence, city (100%)
- year, month, and day of death (95% of deceased)
- birth registration number (95% if born in B.C.)

Access

Policy
- established policy and procedure, which may change in 1993

Procedure
- application to director for approval — detailing project, research proposal, grant, other funding sources, and confidentiality "contract"

Type of access
- indirect, by the Division of Vital Statistics

Resources available
- software (customized), machine time, and experienced personnel

Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Ron Danderfer, Executive Director (604) 387-4807



British Columbia Linked Health Data Project

Centre for Health Services and Policy Research
University of British Columbia
429 - 2194 Health Sciences Mall
Vancouver, British Columbia
V5T 1Z3

General Characteristics

Purpose	• to undertake a major linkage of the B.C. Ministry of Health files, when completed (approximately 1995); six files (hospital separations, medical services, long-term care, pharmacare, births and deaths) will be indexed with a common individual care recipient identifier, to allow linkages between these files to be carried out in a relatively simple manner
Relevant content	• will make linked access possible for information on hospital separations files, eligible medical services under the B.C. Medical Services Plan, inpatient, day program and home care services provided by the B.C. Continuing Care Services and vital statistics
Target population	• B.C. resident population
Coverage	• known bias, a small portion of the population is not covered by the Medial Services Plan • estimated proportion of the target population included is 100%
Data collection	• based on data from ongoing data collection process, updated annually
Time period	• data will be linked for 1985 to the present, with an unlimited retention period

Size

- in 1990-91 approximately:

  700 000 hospital separations
  55 million medical services
  800 megabytes of long-term care files
  75 000 vital statistics records

Unit of analysis

- event, with common individual care recipient identifier

Technical Characteristics

Data storage

- in machine-readable form as raw data (EBCDIC)

Previous record linkage

- created through record linkage

*Identifying variables (approximate percentage of records)**

- surname (100% — Long-Term Care, Vital Statistics)
- first given name (100% — Long-Term Care, Vital Statistics)
- sex (100%)
- marital status (100%)
- year, month, and day of birth (100%)
- birth province or country (100% — Vital Statistics)
- birth city or place (100% — Vital Statistics)
- own place of residence, province or country (100%)
- postal code (100%)
- year, month, and day of death (100% of deceased)
- health insurance number (100%)

* The presence of each identifier and proportion of records varies as is briefly indicated here.

Access

Policy	• established policy and procedure
Procedure	• application for permission from the appropriate division of the B.C. Ministry of Health: Medical Services Plan Hospital Care Division Continuing Care Division Division of Vital Statistics
Type of access	• indirect
Resources available	• software (custom), machine time, and experienced personnel
Costs	• quote prepared for each request
Contact person	• Richard Chamberlayne, Project Manager (604) 822-6668



British Columbia Perinatal Data Base

Centre for Health Services and Policy Research
University of British Columbia
Vancouver, British Columbia
V6T 1Z6

General Characteristics

Purpose
- for a research project comparing perinatal outcome in the province of British Columbia to that in the state of Washington

Relevant content
- contains medical service utilization information in combination with maternal health problems during pregnancy and newborn outcome (birthweight, gestational age, diagnostic information), and mortality information

Target population
- all births in British Columbia from 1986 to 1989

Coverage
- 94% link of medical service, hospital discharge, and vital statistics information; unlinked cases more likely to be on social assistance, to have poor prenatal care, and low birthweight

Data collection
- one-time, cross-sectional survey

Time period
- data is available for 1987 and 1988, with an unlimited retention period

Size
- 74 000 records in total

Unit of analysis
- events linked to individual

Technical Characteristics

Data storage
- in machine-readable form as a linked file

Previous record linkage

- consists of probabilistic link of medical services, hospital programs, and vital statistics

*Identifying variables (approximate percentage of records)**

- mother's marital status
- mother's year, month, and day of birth
- mother's birth province or country
- baby's year, month, and day of birth
- baby's birth province or country
- postal code
- last known year alive
- year, month, and day of death
- place of death, province or country
- place of death, city
- health insurance number

* Detailed information on each variable not available; overall link was 94 percent.

Access

Policy

- established policy and procedure

Procedure

- application to the Centre for Health Services and Policy Research

Type of access

- negotiated

Resources available

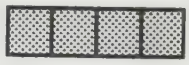
- software, machine time, and experienced personnel

Costs

- quote prepared for each request

Contact person

- Dr. Robert Armstrong, Department of Pediatrics, Sunny Hill Hospital, 3644 Flocan Street, Vancouver, British Columbia, V5M 3E8 (604) 433-4449



British Columbia Vital Statistics (VSTATS)

Division of Vital Statistics
Ministry of Health
818 Fort Street, 3rd Floor
Victoria, British Columbia
V8W 1H8

General Characteristics

Purpose

- location and verification of personal vital event data for the issuance of certificates, and research concerning natality, mortality, fertility, health status, mapping, etc.

Relevant content

- birth and stillbirth data, such as date and place of birth, marital status of mother, age and birthplace of parents, duration of pregnancy, birthweight, kind of birth (twins, etc.), birth order, immediate cause of stillbirth, antecedent cause, autopsy, point of death, etc.
- perinatal conditions (includes congenital defects) and maternal complications, etc.
- death data such as date and place of death, marital status, sex, origin, immediate cause of death, antecedent cause of death, autopsy, etc.

Target population

- all registrations and physicians' notices of birth, no exclusions

Coverage

- overall response rate is 100%
- no known biases; estimated proportion of the target population included is 100%

Data collection

- ongoing data collection process, updated daily with a monthly edit; approximately 385 added each day

Time period
- data are available for 1950-1991, with an unlimited retention period

Size
- approximately 75 000 records a year, 3 million records in total

Unit of analysis
- individuals and events

Technical Characteristics

Data storage
- in machine-readable form as raw data (EBCDIC) and as software-defined SQLDS and dBase II data bases

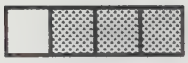
Previous record linkage
- has been linked internally — for example, birth and infant deaths — and externally to the MSP Indian files and for other special projects

Identifying variables (approximate percentage of records)

- surname (100%)
- first given name (100%)
- second given name (95%)
- sex (100%)
- marital status (100%)
- year, month, and day of birth (100%)
- birth province or country (100%)
- birth city (100%)
- father's surname (100%)
- father's first given name (100%)
- father's second given name (90%)
- father's birth province or country (100%)
- mother's maiden name (100%)
- mother's first given name (100%)
- mother's second given name (100%)
- mother's birth province or country (100%)
- own place of residence, province (100%)
- own place of residence, city (100%)
- postal code of residence (95%)
- last year known alive (100%)
- year, month, and day of death (100%)
- place of death, province or country (100%)
- place of death, city (100%)
- death registration number (100%)
- health insurance number (10-20%)

Access

Policy	• established policy and procedure, which may change in 1993
Procedure	• application to director for approval — detailing project, research proposal, grant, other funding sources, and confidentiality "contract"
Type of access	• indirect, by the Division of Vital Statistics
Resources available	• software (customized), machine time, and experienced personnel
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Dr. R.J. Danderfer, Executive Director (604) 387-4807



Canada Fitness Survey 1981 and Follow-Up 1988
(Campbell's Survey on Well-Being in Canada 1988)

Canadian Fitness and Lifestyle Research Institute
Suite 313, 1600 James Naismith
Gloucester, Ontario
K1B 5N4

General Characteristics

Purpose

- to provide baseline data on physical activity and fitness, and normative data on physical measurements; a longitudinal follow-up of a subsample with comparable data for 1981 and 1988

Relevant content

- includes variables measuring physical fitness, activity, attitudes and knowledge, barriers, modifiers, including alcohol and tobacco use, nutrition, and current health, plus demographics and socioeconomic status
- death data; immediate cause of death for 1981 file

Target population

- non-institutionalized Canadian population aged 7 to 69, excluding the Northwest Territories, Yukon, Indian reserves, and remote areas as defined by the Canadian Labour Force Survey (approximately 3%)

Coverage

- no known bias
- original survey is a stratified, multiple cluster sample of 13 440 households, containing 34 363 individuals, with a 76% response rate
- weighting is required to be representative

- estimated proportion of the target population included is approximately 0.001%, less for the follow-up

Data collection

- cross-sectional survey involving direct measurement, a self-administered questionnaire, an interview, and observation
- longitudinal follow-up of 20% of the sample was done in 1988 — the Campbell's Survey on Well-Being in Canada

Time period

- data is available for 1981, plus 1988 follow-up, with an unlimited retention period

Size

- 23 400 records in total, from 7 532 households in 1981
- 4 345 records in the 1988 follow-up

Unit of analysis

- individual

Technical Characteristics

Data storage

- in machine-readable form (EBCDIC) as public-use microdata file

Previous record linkage

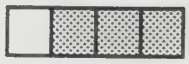
- 1981 file previously linked to the Canadian Mortality Data Base

Identifying variables (approximate percentage of records)

- surname (80%)
- first given name (80%)
- sex (100%)
- marital status (95-100%)
- year of birth (80-100%)
- month of birth (80-100%)
- birth province or country (100%)
- own place of residence, province (80-100%)
- own place of residence, city (80-100%)

Access

Policy	• no established policy and procedure, dealt with on an ad hoc basis
Procedure	• record linkage requests to be submitted in writing, explaining need, confidentiality safeguards, access by others, and use of the data
Type of access	• negotiated
Resources available	• none
Costs	• quote prepared for each request
Contact person	• Cora Craig, Executive Director (613) 748-5791



Canada Health Survey (CHS) 1978-79

Canadian Centre for Health Information
Statistics Canada
R.H. Coats Building, 18th Floor
Tunney's Pasture
Ottawa, Ontario
K1A 0T6

General Characteristics

Purpose

- population-based sample survey to assess the health status of the population and to assist in the planning of health care, health promotion, and prevention

Relevant content

- numerous variables measuring risk factors (such as alcohol and tobacco use, physical activity, and blood levels of lead, copper, and other heavy metals), health status and consequences, and associated sociodemographic characteristics

Target population

- non-institutionalized Canadian population, excluding the Northwest Territories, Yukon, Indian reserves, and remote provincial areas with a low population density; the excluded population represents approximately 3% of the total Canadian population

Coverage

- sampled 12 000 households, containing 40 000 individuals, with a response rate ranging from 72% to 89%, depending on the survey instrument
- weighting is required to be representative
- estimated proportion of the target population included is approximately 0.18% or less, depending on the survey instrument

Data collection

- one-time, cross-sectional survey, involving three questionnaire components and a

biomedical assessment for a subsample of the population (see size below)

Time period
- data are available for 1978-79, with an unlimited retention period

Size
- number of records depends on the survey component:
  - 31 668 individuals for the interviewer-administered questionnaire focussing on health status and consequences
  - 23 791 individuals for the self-administered questionnaire focussing on risk factors
  - 5 662 individuals for the physical measures component of which 4 829 individuals voluntarily provided blood samples

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as raw data and as a public-use microdata file

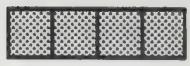
Previous record linkage
- previously linked to the Canadian Mortality Data Base

Identifying variables (approximate percentage of records)

- surname (99.9%)
- first given name (99.9%)
- second given name (3.7%)
- sex (100%)
- marital status (99.7%)
- year of birth (100%)
- month of birth (99.7%)
- day of birth (67.6%)
- birth province or country (99.4%)
- own place of residence, province (100%)
- own place of residence, city (100%)
- last year known alive (100%)

Access

Policy	• established policy and procedure
Procedure	• record linkage requests can be submitted through the contact person subject to Statistics Canada Record Linkage Policy Committee and approval by the minister responsible for Statistics Canada
Type of access	• indirect, by Statistics Canada only
Resources available	• software GRLS, machine time, and experienced personnel
Costs	• quote prepared for each request
Contact person	• Nelson Nault, Manager, Information Requests Unit (613) 951-1746



Canadian Birth Data Base (CBDB)

Occupational and Environmental Health Research Section
Station 18Q
Canadian Centre for Health Information
Statistics Canada
R.H. Coats Building, 18th Floor
Tunney's Pasture
Ottawa, Ontario
K1A 0T6

General Characteristics

Purpose

- this data base is currently in the pilot stage as a special project, which will be completed in March 1994
- for national historical record linkage studies and epidemiology studies
- based on the Integrated Vital Statistics (IVS) data base

Relevant content

- birth and stillbirth data such as date and place of birth, marital status of mother, age and ethnicity of parents, duration of pregnancy, birthweight, kind of birth (twins, etc.), birth order, immediate cause of stillbirth, antecedent cause, autopsy, point of death, etc.

Target population

- all live birth and stillbirth registrations occurring in Canada

Coverage

- overall response rate is approximately 100%
- no known bias
- estimated proportion of the target population included is approximately 100%

Data collection

- ongoing data collection process, at present only for three years

Time period
- data will be available for 1987-1989, with an unlimited retention period
- earlier data can be made available at considerable additional cost

Size
- approximately 1.1 million records in total

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form

Previous record linkage
- none at present, planned in future

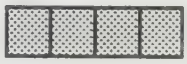
*Identifying variables (approximate percentage of records)**

- surname
- first given name
- first initial
- second given name
- sex
- marital status
- year, month, and day of birth
- birth province or country
- father's surname
- father's first initial
- father's birth province or country
- mother's maiden name
- mother's first initial
- mother's birth province or country
- mother's place of residence, province
- mother's place of residence, city
- year, month, and day of death
- place of death, province or country
- place of death, city
- birth registration number (stillbirth/live birth)

* The availability of identifying variables varies by year and province and has yet to be ascertained.

Access

Policy	• established policy and procedure
Procedure	• record linkage requests can be submitted through the contact person subject to Statistics Canada Record Linkage Policy Committee and approval by the minister responsible for Statistics Canada
Type of Access	• indirect, by Statistics Canada only
Resources available	• software (GRLS), machine time, and experienced personnel
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Martha Fair, Chief (613) 951-1734



Canadian Cancer Data Base (CCDB)

Occupational and Environmental Health Research Section
Station 18Q
Canadian Centre for Health Statistics
Statistics Canada
R.H. Coats Building, 18th Floor
Tunney's Pasture
Ottawa, Ontario
K1A 0T6

General Characteristics

Purpose

- for national, historical, cancer-incidence record linkage studies, and epidemiology studies
- prepared from the National Cancer Incidence Reporting System in a standard format suitable for record linkage

Relevant content

- diagnoses of all neoplasms (ICD-9 140-239) excluding benign (ICD-9 210-229), date of diagnosis, method of diagnosis, age at diagnosis, primary site, topography, morphology, etc.

Target population

- all cancer-incident events occurring in Canada

Coverage

- overall response rate is 100% of provincial data
- some under-registration and over-registration in some provinces
- estimated proportion of the target population included is approximately 95%

Data collection

- ongoing data collection process, updated annually

Time period
- data is available for 1970-1986 (1987-88 being processed), with an unlimited retention period

Size
- approximately 1.2 million records

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form

Previous record linkage
- has been linked to a data base of tuberculosis patients who received fluoroscopy treatment and is presently being linked to a data base of farmers (pesticide exposure) and the Nutrition Canada Survey

*Identifying variables (approximate percentage of records)**

- surname (100%)
- alternate surname ever used (4-13.4%)
- first given name (99.5%)
- first initial (99.9%)
- second given name (25.8%)
- second initial (33%)
- sex (100%)
- marital status (34.5%)
- year of birth (99.9%)
- month of birth (88.8%)
- day of birth (86.2%)
- birth province or country (24.2%)
- own place of residence, province (100%)
- own place of residence, city (32.5%)
- postal code (24.9%)
- year of death (24.3%)
- month of death (22.8%)
- day of death (22.8%)
- death registration number (19.8%)
- health insurance number (62.2%)

* The availability of identifying variables varies by year and province.

Access

Policy	• established policy and procedure
Procedure	• record linkage requests can be submitted through the contact person subject to Statistics Canada Record Linkage Policy Committee and approval by the minister responsible for Statistics Canada
Type of access	• indirect, by Statistics Canada only
Resources available	• software (GRLS.V1), machine time, and experienced personnel
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Martha Fair, Chief (613) 951-1734



Canadian Congenital Anomalies Surveillance System (CCASS)

Laboratory Centre for Disease Control
Health and Welfare Canada
Basement, Health Protection Building
Tunney's Pasture
Ottawa, Ontario
K1A 0L2

General Characteristics

Purpose	• passive surveillance of birth defects
Relevant content	• hospital diagnoses of congenital anomalies as found in Chapter 14 of the International Classification of Diseases (ICD-9), codes 740-759
Target population	• births in hospitals affiliated with the Hospital Medical Records Institute (HMRI) — about 80% of Canadian hospital discharges
Coverage	• overall response rate is 100%
	• known bias — excludes births outside hospitals, participating hospitals tend to be teaching hospitals in provinces where coverage is incomplete
	• estimated proportion of the target population included is 79%
Data collection	• ongoing data collection process, updated annually
Time period	• data is available for 1970-1990, with an unlimited retention period
Size	• approximately 174 516 records in total
Unit of analysis	• individual

Technical Characteristics

Data storage
- in machine-readable form as a raw data file or a software-defined data base

Previous record linkage
- has been linked to Ontario Vital Statistics (births) and the Ontario Cancer Registry

Identifying variables (approximate percentage of records)

- sex (90%)
- year, month, and day of birth (100%)
- birth province or country (100%)
- birth city or place (40%)
- own place of residence, province (100%)
- own place of residence, city (40%)
- postal code (40%)
- year, month, and day of death (9%)
- place of death, province or country (100%)
- place of death, city (40%)
- health insurance number (100%)

Access

Policy
- no established policy and procedure

Procedure
- permission from HMRI and from the provincial governments who supplied the data

Type of access
- to be negotiated

Resources available
- resources are presently not available due to over-commitment

Costs
- none

Contact person
- Tye Arbuckle (613) 941-1287



Canadian Infertility Therapy Evaluation Study (CITES)

Department of Obstetrics and Gynaecology
McMaster University Medical Centre
1200 Main Street West, Room 4D9
Hamilton, Ontario
L8N 3Z5

General Characteristics

Purpose

- to determine the distribution of clinical characteristics of infertile couples registered in Canadian health science centre infertility clinics and to evaluate the treatment given and outcome during 36 months following registration (the follow-up was extended to cover 1988-1991 for 75% of the couples)

Relevant content

- information on male and female partners' history, physical examination and investigations (including hysterosalpingogram), semen analysis, hysteroscopy, ovulation tests, and laparoscopy, diagnostic summary, and follow-ups, including present status, pregnancy follow-up, and treatment status of the male and female partner, listing interventions, etc.

Target population

- infertile couples with a complaint of infertility of more than 12 months' duration registered with hospitals at the participating universities (University of British Columbia, Calgary, Western, McMaster, Queen's, Ottawa, McGill, Laval, Saskatchewan, Sherbrooke, and Dalhousie), excluding couples where either partner had undergone sterilization

Coverage

- known bias — includes only couples referred to the participating health science centres
- estimated proportion of the target population included is unknown

Data collection
- longitudinal survey that follows the same group of respondents with a variable follow-up period

Time period
- data is available for 1984-1991, with an unlimited retention period

Size
- 2 198 records in total

Unit of analysis
- couple

Technical Characteristics

Data storage
- in machine-readable form as raw data and as a software-defined data base

Previous record linkage
- none

Identifying variables (approximate percentage of records)

- sex (100%)
- year, month, and day of birth (100%)
- postal code (60%)
- female partner's surname (70%)*
- female partner's given name (70%)*
- male partner's surname (70%)*
- male partner's given name (70%)*

* These are not included in the data base but are available from the individual centres.

Access

Policy
- no established policy and procedure

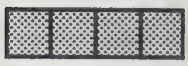
Procedure
- application to Dr. J.A. Collins

Type of access
- indirect

Resources available
- software (SPSS, SAS), machine time, and experienced personnel

Costs
- quote prepared for each request

Contact person
- Dr. J.A. Collins (905) 525-9140 ext. 22566



Canadian Mortality Data Base (CMDB)

Occupational and Environmental Health Research Section
Canadian Centre for Health Information
R.H. Coats Building, 18th Floor
Tunney's Pasture
Ottawa, Ontario
K1A 0T6

General Characteristics

Purpose	• for national historical mortality record linkage studies, epidemiology studies, and generation of other statistical products
	• based on the Integrated Vital Statistics (IVS) data base
Relevant content	• mortality data such as date and place of death, marital status, sex, province or country of birth, underlying cause of death, autopsy, etc.
Target population	• all death events occurring in Canada, and deaths of Canadian residents occurring in the United States
Coverage	• no known bias — estimated proportion of the target population included is approximately 100%
Data collection	• ongoing data collection process, updated annually
Time period	• data is available for 1950-1989, with an unlimited retention period
Size	• approximately 6.25 million deaths (7.9 million records) in total
Unit of analysis	• individual

Technical Characteristics

Data storage
- in machine-readable form and on microfilm

Previous record linkage
- has been linked for assorted research uses, too numerous to list

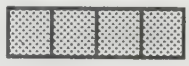
*Identifying variables (approximate percentage of records)**

- surname (100%)
- alternate surname ever used (1.2%)
- first given name (98.3%)
- first initial (98.4%)
- second given name (44.8%)
- second initial (47.5%)
- sex (100%)
- marital status (99%)
- year of birth (99.9%)
- month of birth (85.7%)
- day of birth (85.2%)
- birth province or country (67.3%)
- father's surname (72.9-99%)
- father's first given name (85%)
- father's first initial (60.4-84%)
- father's second name (13%)
- father's second initial (9.3-12.5%)
- father's birth province or country (46.6%)
- mother's maiden name (46.7-65%)
- mother's first given name (80%)
- mother's first initial (50.5-70%)
- mother's birth province or country (45.8%)
- own place of residence, province (99.9%)
- own place of residence, city (90-99%)
- last year known alive (100%)
- year, month, and day of death (100%)
- place of death, province or country (100%)
- place of death, city (93-95.8%)
- social insurance number (25%)
- death registration number (100%)

* Availability of identifying variables varies by year and province.

Access

Policy	• established policy and procedure
Procedure	• record linkage requests can be submitted through the contact person subject to Statistics Canada Record Linkage Policy Committee and approval by the minister responsible for Statistics Canada
Type of access	• indirect, by Statistics Canada only
Resources available	• software (GRLS), machine time, and experienced personnel
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Martha Fair, Chief (613) 951-1734



Quebec Cancer Registry (Déclarations des tumeurs [Québec])

2 Ministère de la Santé et des Services sociaux
1179, boul. Charest ouest
Québec (Québec)
G1N 4K7

General Characteristics

Purpose	•	to follow the development of new cases of cancer
Relevant content	•	type of residence, date of admission, diagnosis, method of diagnosis, location and type of tumour (ICD-9 codes 140-208), date of discharge
Target population	•	all Quebec residents who are hospitalized with a cancer diagnosis in an acute care hospital
Coverage	•	known bias — only those in acute care hospitals
	•	estimated proportion of the target population included is 55% (1975-1981) and 99% (1982-89)
Data collection	•	ongoing data collection process, updated as each new event occurs
Time period	•	data available for 1975-1989, with an unlimited retention period
Size	•	approximately 25 000 new cases per year
Unit of analysis	•	event

Technical Characteristics

Data storage	•	in machine-readable form as raw data

Previous record linkage
- Med-Echo hospitalization records file

Identifying variables (approximate percentage of records)
- surname (100%)
- first given name (100%)
- sex (100%)
- marital status (100%)
- year, month, and day of birth (100%)
- birth province or country (100%)
- birth city or place (100%)
- father's first given name (100%)
- mother's maiden name (100%)
- mother's first given name (100%)
- own place of residence, province or country (100%)
- own place of residence, city (100%)
- postal code (100%)
- health insurance number (100%)

Access

Policy
- established policy and procedure

Procedure
- detailed requests to be submitted in writing, and may be subject to the approval of the Information Access Commission

Type of access
- negotiated

Resources available
- software (data base), machine time, and experienced personnel

Costs
- have a fee schedule

Contact person
- Lorraine Nadeau (418) 643-6209



Easter Seal Client Registry

Easter Seal Society
250 Ferrand Drive, Suite 200
Don Mills, Ontario
M3C 3P2

General Characteristics

Purpose

- to provide the Easter Seal Society with a more adequate picture of children in the active case load, in particular to highlight principal characteristics of new and active cases to provide a profile of needs for specialized services

Relevant content

- demographics, up to eight diagnoses in coded form (ICD-9), all diagnoses described in English, etiology of condition, whether the condition was congenital, acquired (i.e., due to infections, neoplasms, stroke), or traumatic, treatment centres attended, facilities and services, and whether they are required, not required, met or unmet (i.e., physio/speech therapy, medical treatment, infant stimulation, transportation, respite care, home care, residential care, family support worker, home renovation, life skills, recreation and leisure, etc.), languages, living arrangement, etc.

Target population

- persons who live within Ontario under the age of 19 years whose restriction of activity by reason of neurological, musculoskeletal, or other organic defects produces a physical handicap (i.e., who fall within the general mandate of the Easter Seal Society of Ontario)

Coverage

- based on Easter Seal nurse's assessment
- estimated proportion of the target population included is unknown

Data collection
- ongoing process, approximately 50-100 cases registered each month, follow-up data collected on active cases on timely basis

Time period
- data will be available from computer for 1990 to present; 1970-1989 has to be extracted manually from hard copies

Size
- approximately 7 500 active records in 1992

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form since 1990, older files can be manually retrieved

Previous record linkage
- none

Identifying variables (approximate percentage of records)

- surname (100%)
- first given name (100%)
- sex (100%)
- year, month, and day of birth (100%)
- place of residence (village, town or county/district/regional municipality) (100%)
- registration number (100%)

Access

Policy
- none, only statistical information has been released to date

Procedure
- none, situation has not arisen

Type of access
- indirect

Resources available
- none

Costs
- to be negotiated

Contact person
- Ms Asha Nambyarooran, Registry Coordinator (416) 421-8377



Quebec Health Survey (Enquête Santé [Québec]) 1987

600 ouest, boul. René Lévesque
10ième étage
Montréal Québec
H3B 1N4

General Characteristics

Purpose

- to gather information on mental and physical health of the population of Quebec to complement existing information

Relevant content

- includes information on family health history, life events, psychological health, lifestyle variables such as alcohol and tobacco use, physical activity, drug use, sleep problems, health prevention practices (e.g., pap smear, mammography screening) and perceived health

Target population

- Quebec population living in private homes, excludes those living in institutions and persons living in remote northern areas

Coverage

- sampled 1:200, with an overall response rate of approximately 80%
- weighting is required to be representative
- 300 households by DSC and 900 households by region (11)

Data collection

- one-time cross-sectional survey, involving two questionnaires, one administered by an interviewer, the other self-administered

Time period

- data are available for 1987, with an unlimited retention period

Size

- 32 000 records in total, 16 000 in machine-readable form

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as new data

Previous record linkage
- linked with the data of the Régie d'assurance-maladie du Québec

Identifying variables (approximate percentage of records)

- surname* (100%)
- first given name* (100%)
- sex (100%)
- year, month, and day of birth (100%)
- own place of residence, province (90%)
- own place of residence, city (90%)
- postal code (63-99%)
- DSC (100%)

* These identifiers have been collected for all households and respondents but are kept in a separate file at the Bureau de la statistique du Québec with very limited access.

Access

Policy
- established policy and procedure

Procedure
- for linkage, an agreement must be reached with Santé Québec

Type of access
- negotiated

Resources available
- software (data base), machine time, and experienced personnel

Costs
- no fees

Contact person
- Aline Émonde (514) 873-4749



General Social Survey (GSS-6) 1991

General Social Survey
Statistics Canada
R.H. Coats Building
Tunney's Pasture
Ottawa, Ontario
K1A 0T6

General Characteristics

Purpose

- part of the General Social Survey project, intended to collect information on health status, lifestyle, risk factors, and health care utilization

Relevant content

- health status, lifestyle, and risk factors including alcohol and tobacco use, occupation and industry, occupational exposure to specific factors, plus health care utilization, demographics, and socioeconomic status

Target population

- non-institutionalized Canadian population, 15 years of age and older, living in Canada's 10 provinces

Coverage

- known biases — those without telephones who tend to be in the low income group, less than 3% of the population
- sampled 1:2 000, with an 80% response rate
- weighting is required to be representative
- estimated proportion of the target population included in the household survey is less than 0.01%

Data collection

- repeated cross-sectional survey, with a longitudinal component, collected annually, focussing on health every fifth year

Time period
- data available for 1991, with an unlimited retention period

Size
- 11 924 records in total

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as raw data

Previous record Llnkage
- pilot link of the longitudinal component to the 1990 General Social Survey, Cycle 5

Identifying Variables (approximate percentage of records)

- surname (84%)
- first given name (84%)
- sex (100%)
- marital status (100%)
- year of birth (100%)
- month of birth (97%)
- day of birth (97%)
- birth province or country (98%)
- own place of residence, province (100%)
- own place of residence, city (84%)
- postal code (94%)
- telephone number (100%)

Access

Policy
- established policy and procedure

Procedure
- detailed record linkage requests to be submitted in writing, and are subject to the approval of the Statistics Canada Data Linkage Committee, the chief statistician, the minister, and possibly the privacy commissioner

Type of access
- indirect, by Statistics Canada only

Resources available
- software (GRLS), machine time, and experienced personnel

Costs
- quote prepared for each request

Contact person
- Ed Praught (613) 951-9180



Hospital Medical Records Institute Data Bases (HMRI)

Hospital Medical Records Institute Data Bases
250 Ferrand Drive, 5th Floor
P.O. Box 3900
Don Mills, Ontario
M3C 2T9

General Characteristics

Purpose

- administrative data base for hospital management purposes and creation of provincial morbidity data bases: Inpatient Data Base and Day Surgery Data Base

Relevant content

- hospital morbidity including admission diagnosis, primary and secondary diagnoses coded using the International Classification of Diseases (ICD-9), primary and secondary procedures coded using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP)

Target population

- discharges from HMRI client hospitals (primarily acute care inpatients and day surgery visits); excludes emergency room visits, clinic visits, and discharges from non-HMRI hospitals

Coverage

- known biases — in provinces with less than 100% participation, clients are more likely to be large teaching hospitals; the most significant gaps in the HMRI acute care data base are in Manitoba, Quebec, and Nova Scotia
- estimated proportion of the target population included is 80% of total Canadian hospital discharges

Data collection

- ongoing data collection process, updated monthly with approximately 350 000 records added each month

Time period
- data available 1979-1991, varying by province, with an unlimited retention period

Size
- 4.2 million records on average each year

Unit of analysis
- event, discharges

Technical Characteristics

Data storage
- in machine-readable form as raw data for all years, and for the last two years as a software-defined data base

Previous record linkage
- previous linkage to OHIP and Compusearch data bases

Identifying variables (approximate percentage of records)

- sex (100%)
- year of birth (100%)
- month of birth (100%)
- day of birth (100%)
- own place of residence, province (100%)
- own place of residence, city (100%)
- postal code (100%)
- year, month, and day of death (3%)
- place of death, province or country (3%)
- place of death, city (3%)
- health insurance number (100%)
- hospital identifier (100%)

Access

Policy
- established policy and procedure

Procedure
- contact the HMRI, Special Needs Applications Program if access to sensitive data elements is requested, the client completes a request form and submits it for consideration; if identifiers are requested, the request must also be approved by the institution that provided the data to HMRI

Type of access
- negotiated

Resources available	• machine time
Costs	• have a fee schedule, and a quote is prepared for each request
Contact person	• Chris Helyar, Vice-President (416) 429-1953 • Isabel Tsui, Manager, Application Development (416) 429-1953



In-Vitro Fertilization (IVF) Registry

Canadian Voluntary Regulatory Association
1053 Carling Avenue, Suite 570
Ottawa, Ontario
K1Y 4E9

General Characteristics

Purpose	• to collect case data on each IVF attempt in Canada including outcome of treatment, normality of infants, and morbidity
Relevant content	• brief relevant patient medical history, age, planned therapy, semen characteristics, stimulation drugs, cycle monitoring information, (e.g., retrieval/per embryo transfer, luteal phase support, pregnancy monitoring, embryo inventory, pregnancy outcome, maternal complications, etc).
Target population	• patients of IVF clinics in Canada
Coverage	• overall response rate is 100% • no known bias • estimated proportion of the target population included is 100%
Data collection	• ongoing data collection process, updated quarterly
Time period	• data are available for 1991-92, with an unlimited retention period
Size	• approximately 4 000 records a year, each record comprising a treatment cycle (about 1 500 to 2 000 women a year)
Unit of analysis	• individual

Technical Characteristics

Data storage
- in machine-readable form as a Paradox data base

Previous record linkage
- none

Identifying variables (approximate percentage of records)

- first given initial (100%)
- second given initial (100%)
- sex (100%)
- year, month, and day of birth (100%)
- own place of residence, province (100%)
- own place of residence, city (100%)
- last known year alive (100%)
- health insurance number (100%)
- case record number (100%)

Access

Policy
- established policy and procedure

Procedure
- apply to CVRA executive

Type of access
- indirect, in some cases negotiated

Resources available
- software, machine time, and experienced personnel

Costs
- quote prepared for each request

Contact person
- Dr. Arthur Leader, Director (613) 761-4427



Manitoba Chlamydia Data Base

730 William Avenue, Room 503
University of Manitoba
Winnipeg, Manitoba
R3E 0W3

General Characteristics

Purpose	• to link positive laboratory reports for chlamydia trachomatis in females to medical insurance billing claims data in order to determine the incidence of the sequelae of genital infection
Relevant content	• demographics such as age and sex, reproductive variables such as ectopic pregnancy, infertility, and pelvic inflammatory disease (ICD-9)
Target population	• Manitoba females, age 15 to 44 with positive and negative test results for genital chlamydia trachomatis (submitted to Cadham Provincial Laboratory)
Coverage	• no known bias • estimated proportion of the target population included is 85%
Data collection	• longitudinal study of positive reports from 1984 to 1989, followed to December 1989
Time period	• data will be available for positive reports from 1984 to 1989, with an unlimited retention period
Size	• approximately 18 000 records in total
Unit of analysis	• event, diagnosis

Technical Characteristics

Data storage
- in machine-readable form as raw data

Previous record linkage
- Manitoba Health Services Commission Hospital and physician billings

Identifying variables (approximate percentage of records)

- sex (100%)
- year, month, and day of birth (80%)
- postal code (30%)
- health insurance number (85%)

Access

Policy
- highly confidential material, at present access restricted to researchers of the Manitoba Centre for Health Policy and Evaluation

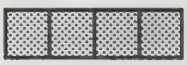
Procedure
- detailed requests to be submitted in writing, and are subject to the approval of the Manitoba Health Services Commission, the Cadham Provincial Laboratory, and the University of Manitoba

Type of access
- not yet specified, data base is just being formulated

Resources available
- software, machine time, and experienced personnel

Costs
- quote prepared for each request

Contact person
- Dr. P.H. Orr, Professor (204) 788-6357



Manitoba Permanent Medical Statistical File

Management Information Systems
Manitoba Health
Box 925
599 Empress Street
Winnipeg, Manitoba
R3C 2T6

General Characteristics

Purpose	• to provide a permanent statistical record of insured medical services by health care practitioners and to generate payments to providers of these services
Relevant content	• physician claims for services rendered, procedures in the form of a Manitoba tariff code, and a three-digit ICD-9 diagnosis code
Target population	• permanent residents of Manitoba; excludes military and RCMP personnel and inmates of federal institutions
Coverage	• known bias — exclusions mentioned above • estimated proportion of the target population included is approximately 85%
Data collection	• ongoing data collection process, updated monthly • approximately 1 million records are added each month
Time period	• data are available for 1969-1992, with a limited retention period of 30 years
Size	• 13 million records a year, 286 million in total
Unit of analysis	• events

Technical Characteristics

Data storage
- in machine-readable form as raw data file

Previous record linkage
- previously linked to the Hospital Abstract System and Population Data Base

Identifying variables (approximate percentage of records)

- first five characters of surname (100%)
- first initial (100%)
- sex (100%)
- year of birth (100%)
- month of birth (100%, 1984+)
- own place of residence (100%)
- health insurance number (100%, 1984+)

Access

Policy
- established policy and procedure

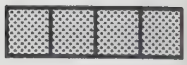
Procedure
- written application to the Access and Confidentiality Committee, which makes recommendations on access to executive management

Type of access
- negotiated

Resources available
- software, machine time, and experienced personnel available; or the Manitoba Centre for Health Policy and Evaluation at the University of Manitoba with special permission

Costs
- quote prepared for each request

Contact person
- Guenter Bormann, Manager (204) 786-7343



Nova Scotia Perinatal Data Base

Nova Scotia Reproductive Care Program
5821 University Avenue
Halifax, Nova Scotia
B3H 1W3

General Characteristics

Purpose
- used as a clinical audit and for research of perinatal events

Relevant content
- includes demographic and delivery data on mother and baby, information on previous maternal diseases, maternal diseases during the present pregnancy, therapy, and procedures (including infertility procedures), and infant diseases, anomalies, and treatments given during hospitalization

Target population
- all deliveries that occur in hospital in Nova Scotia including live births and stillbirths over 500 grams

Coverage
- overall response rate is 100%
- known bias is the exclusion of home births which are a very small proportion of total births
- estimated proportion of the target population included is 100%

Data collection
- ongoing data collection process, updated at varying intervals ranging from three to twelve months depending on the hospital

Time period
- data are currently available for 1988-1990; collection is ongoing with an unlimited retention period

Size
- approximately 12 000 records a year

Unit of analysis
- mother and baby

Technical Characteristics

Data storage
- in machine-readable form as a SIR data base

Previous record linkage
- none

Identifying variables (approximate percentage of records):

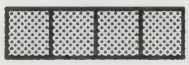
- baby's surname* (100%)
- baby's first given name* (50%)
- baby's sex (100%)
- baby's year, month, and day of birth (100%)
- baby's birth province or country (100%)
- mother's married name* (100%)
- mother's maiden name* (75%)
- mother's first given name* (100%)
- mother's first initial* (100%)
- mother's second given name* (50%)
- mother's second initial* (80%)
- mother's marital status (100%)
- mother's year, month, and day of birth (99%)
- own place of residence, province (99%)
- own place of residence, city (99%)
- postal code (99%)
- baby's year, month, and day of death, if before age 1 (95%)
- baby's place of death, province or country, if before age 1 and if baby died in Nova Scotia (95%)
- health insurance number* (90%)

* For purposes of confidentiality, these variables are not contained in the data base. With appropriate permission this information is retrievable and can be linked to the data base.

Access

Policy
- no established policy or procedure

Procedure	• permission required from participating hospitals and the Reproductive Care Program Data Administration Committee
Type of access	• indirect, by Reproductive Care Program only
Resources available	• machine time and experienced personnel, no software at this time
Costs	• no policy at this time
Contact person	• Dr. Linda Dodds, Epidemiologist (902) 420-6798



Ontario Health Insurance Plan Detailed Claims File

Information Resources Branch
Ontario Ministry of Health
15 Overlea Boulevard
Toronto, Ontario
M4H 1A9

General Characteristics

Purpose	• to inform senior management of payment claims, trends, practitioner income levels, etc., and to develop specialty profiles, such as age and sex of patients, etc.
Relevant content	• physician claims for procedure-oriented services rendered, include treatments covered by OHIP such as artificial insemination, *in vitro* fertilization, gamete intrafallopian transfer, embryo transfer, intraperitoneal transfer, amniocentesis, chorion biopsy and ultrasound, some diagnoses, and demographics
Target population	• entire population in Ontario; estimated that 85% see physicians
Coverage	• 95% of physicians submit claims • known bias — fee-for-service physicians are not included • estimated proportion of the target population included is approximately 95%
Data collection	• ongoing data collection process, updated monthly • approximately 18-20 million records are added each month
Time period	• data are available for 1986-1992, with a limited retention period of seven years

Size • 250 million records a year

Unit of analysis • claims, records

Technical Characteristics

Data storage • in machine-readable form as raw data file

Previous record linkage • previously linked to HMRI data, the Assistive Devices Program, and Home Care, to name a few

Identifying variables (approximate percentage of records)*

- surname (99%)
- first five letters of first given name (100%)
- sex (100%)
- year, month of birth (100%)
- old insurance number (100%)
- date of service (100%)
- fee schedule code, services, and payments (100%)

* Additional identifiers can be obtained through record linkage.

Access

Policy • established policy and procedure

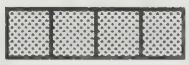
Procedure • written application, each request considered on its own merit

Type of access • negotiated (need to maintain confidentiality — indirect)

Resources available • software, machine time, and experienced personnel

Costs • have a fee schedule and prepare a quote for each request

Contact person • David Bogart, Director (416) 327-7610



Ontario Cancer Registry (OCR)

Ontario Cancer Treatment and Research Foundation
7 Overlea Boulevard
Toronto, Ontario
M4H 1A8

General Characteristics

Purpose	• to provide statistics on the rates and frequencies of cancer incidence for the province of Ontario, and a data base for epidemiological research
Relevant content	• diagnoses of all invasive neoplasms (ICD-9 140-208, excluding non-melanoma skin cancers), date of diagnosis, method of diagnosis, age at diagnosis, primary site, morphology, etc.
Target population	• all cancer patients residing in Ontario newly diagnosed since 1964
Coverage	• estimated proportion of the target population included is over 95%
Data collection	• ongoing data collection process, updated annually
Time period	• data are available for 1964-1989, with an unlimited retention period
Size	• currently 40 000 new cases registered each year
Unit of analysis	• patient based

Technical Characteristics

Data storage	• in machine-readable form as a dBase II relational data base

Previous record linkage
- linked regularly to a variety of study files including occupational and environmental exposure rolls

Identifying variables (approximate percentage of records):

- surname (100%)
- alternate surnames ever used (30%)
- first given name (95%)
- second given name (30%)
- third given name (10%)
- sex (99%)
- year of birth (95%)
- month of birth (88.8%)
- day of birth (80%)
- own place of residence, province (95%)
- own place of residence, city (75%)
- postal code (50%)
- last year known alive (100%)
- year, month, and day of death (100% of deceased)
- place of death, province or country (95% of deceased)
- place of death, city (75% of deceased)
- death registration number (95% of deceased)
- health insurance number (80%)

Access

Policy
- established policy and procedures

Procedure
- access requires a scientific protocol, ethics review and approval, and funding

Type of access
- indirect

Resources available
- software, machine time, and experienced personnel

Costs
- quote prepared for each request

Contact person
- Darlene Dale, Manager of Operations, Cancer Registration Unit (416) 423-4240 ext. 248



Ontario Child Health Study 1983 and Follow-Up 1987

Department of Psychiatry
McMaster University
1200 Main Street West
Hamilton, Ontario
L8S 4J9

General Characteristics

Purpose

- to study the epidemiology of childhood psychiatric disorders, physical health, and substance use in Ontario children

Relevant content

- includes outcome variables measuring psychiatric disorder, perceived need of professional help for emotional problems, and poor school performance, risk factors, such as family dependence on social assistance, lone parent family, or living in subsidized housing, physical health of the child and substance use

Target population

- households with children aged 4 to 16 in 1983; excludes Native reserves, institutions, and buildings constructed after 1981

Coverage

- no known bias
- original survey sampled about 2:1 000 households, with a 91% response rate
- follow-up of children age 4 to 16 at the time of the original study had a response rate of 79%
- weighting is required to be representative
- estimated proportion of the target population included is less than 0.01%

Data collection

- cross-sectional survey

- longitudinal follow-up of children age 4 to 16 at the time the original study was done in 1987

Time period
- data are available for 1983, plus 1987 follow-up, with an unlimited retention period

Size
- 3 294 cases in total comprised of 1 869 households in 1983 and 2 614 cases in the 1987 follow-up

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as software-defined data base

Previous record linkage
- none

Identifying variables (approximate percentage of records)

- surname* (100%)
- first given name* (80%)
- sex* (100%)
- marital status* (100%)
- year of birth* (100%)
- birth province or country (100%)
- father's surname* (70%)
- father's first given name* (70%)
- father's first initial* (70%)
- mother's maiden name* (10%)
- mother's first given name* (100%)

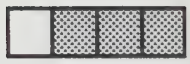
* Identifying variables are held by the Special Survey Division at Statistics Canada and are not in the data base.

Access

Policy
- established policy and procedure

Procedure
- detailed record linkage requests to be submitted in writing to the Special Survey Division at Statistics Canada and are

		subject to Data Linkage Committee, chief statistician, and ministerial approval
Type of access	•	negotiated
Resources available	•	Statistics Canada has software (GRLS), machine time, and experienced personnel
Costs	•	quote prepared by Statistics Canada for each request
Contact person	•	Dr. Michael Boyle (905) 521-2100 ext. 7359



Ontario Health Survey (OHS), 1990

Ontario Ministry of Health
Information Resources Branch
15 Overlea Boulevard, 2nd Floor
Toronto, Ontario
M4H 1A9

General Characteristics

Purpose

- to provide baseline statistical data on the health of the Ontario population, including data for research into the social, economic, physical, behavioural, nutritional, and other factors that contribute to health

Relevant content

- measures of the health status of the population and risk factors for morbidity and mortality in Ontario such as drug, tobacco, and alcohol use, sexual health including the use of contraceptives and a measure of infertility, occupational exposures, physical activity, and nutrition, social, economic, demographic, and geographic variables, awareness of risk behaviour, and utilization of health services

Target population

- all residents of private dwellings in Ontario from January to November 1990, excluding persons in institutions and Natives on reserves

Coverage

- possible bias is yet to be analyzed
- approximately 1 000 persons age 12 and over in each public health unit
- weighting is required to be representative
- estimated proportion of the target population included at the provincial level is approximately 0.6%

Data collection
- one-time cross-sectional survey involving an interview and a self-administered questionnaire

Time period
- data are available for 1990, with an unlimited retention period

Size
- 61 239 records in total

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as raw data (EBCDIC)

Previous record linkage
- plan to link to the Ontario Health Supplement on Mental Health

Identifying variables (approximate percentage of records):

- surname (over 90%)
- first given name (over 90%)
- sex (100%)
- marital status (98%)
- year of birth (99%)
- month of birth (99%)
- day of birth (97%)
- birth province or country (99%)
- father's surname*
- father's first given name*
- father's birth province or country*
- mother's first given name*
- mother's birth province or country*
- own place of residence, province (100%)
- own place of residence, city (100%)

* These identifiers can be derived for some records from household information.

Access

Policy
- established policy and procedure

Procedure	• detailed record linkage requests to be submitted in writing to Statistics Canada, Occupational and Environmental Health Research Section, and will be subject to Statistics Canada Data Linkage Committee, chief statistician, and ministerial approval, and the upcoming Health Information Access and Privacy Act for Ontario
Type of access	• indirect, by Statistics Canada only
Resources available	• Statistics Canada has software (GRLS), machine time, and experienced personnel
Costs	• quote prepared for each request
Contact person	• David Bogart, Director (416) 327-7610



Parents of Multiple Births Association (POMBA) of Canada, Impact of Multiples on the Family Survey 1991

Parents of Multiple Births Association of Canada Inc.
4918 Highway #7 East
Unit 12A, Suite 161
Markham, Ontario
L3R 1N1

General Characteristics

Purpose

- to determine programming needs, development of publications, newsletter topics, and registry needs, and to research the current multiple birth situation to support government lobbying efforts

Relevant content

- demographics, infertility, method of treatment, type of fertility drug used, health insurance coverage, etc.
- new medical questionnaire also includes such variables as past obstetric history, including drugs used; general medical problems; fertility information; reason for multiple pregnancy; number of times medication or other procedures were tried; family history; diagnosis of pregnancy; management of the pregnancy; including use of ultrasound or amniocentesis; exercise and daily activity; hospitalizations prior to delivery; weight gain; diet; use of tobacco and alcohol; pregnancy complications; labour and delivery; complications of infants; hospital course of infants; and post-partum complications

Target population

- Canadian families who have or are expecting twins, triplets, quadruplets, quintuplets, or more

Coverage

- known bias — sent to POMBA members only, tend to be successful pregnancies, for example, all survived within the set
- estimated proportion of the target population included is 10%

Data collection

- repeated survey with different respondents each time, to be conducted every three to five years

Time period

- data will be available for 1991, with an unlimited retention period

Size

- approximately 1 169 records in total

Unit of analysis

- individual families

Technical Characteristics

Data storage

- some in machine-readable form, and on paper

Previous record linkage

- none

Identifying variables (approximate percentage of records)

- baby's surname
- baby's first given name*
- baby's sex*
- baby's year, month, and day of birth*
- parent's marital status
- father's surname*
- father's first given name*
- mother's first given name*
- parent's place of residence, province or country*
- parents's place of residence, city*
- postal code*

* Identifiers are available in non-machine-readable form and are not organized to assess percentage of records at this time.

Access

Policy	•	none at present
Procedure	•	would have to obtain membership approval
Type of access	•	negotiated
Resources available	•	none
Costs	•	to be negotiated
Contact person	•	Ms Donna Launslager (519) 884-1929



Parents of Multiple Births Association (POMBA) of Canada Triplet/Quadruplet/Quintuplet Registry

Parents of Multiple Births Association of Canada Inc.
4918 Highway #7 East
Unit 12A, Suite 161
Markham, Ontario
L3R 1N1

General Characteristics

Purpose

- to create a network of peer and family support for those who have or who are expecting a higher order multiple birth and to provide physicians, health care providers, and families with information about the course and management of these complicated pregnancies

Relevant content

- demographics, such as parents' occupation, children's (multiples and siblings) names, sex, birthweights, and birth dates, gestation period, delivery, months breast-fed, post-natal problems, and other general information
- new medical questionnaire also includes such variables as past obstetric history, drugs used, general medical problems, fertility information, reason for multiple pregnancy, number of times tried medication or procedure, family history, diagnosis of pregnancy, management of the pregnancy, including use of ultrasound, amniocentesis, hospitalizations prior to delivery, weight gain, some diet, use of tobacco and alcohol, pregnancy complications, labour and delivery, complications of infants, hospital course of infants, post-partum complications

Target population

- Canadian families who have or are expecting triplets, quadruplets, quintuplets, or more

Coverage

- known bias — tend to be surviving pregnancies, for example, all survived within the set, also more parents with young children — once children reach 5 or 6 family membership tends to drop
- estimated proportion of the target population included is 15-20%

Data collection

- ongoing process, which will be updated annually

Time period

- data will be available for 1985 to the present, with an unlimited retention period

Size

- approximately 173 member families in total in 1992

Unit of analysis

- individual families

Technical Characteristics

Data storage

- some in machine-readable form, and on file cards

Previous record linkage

- none at present

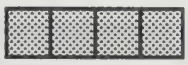
*Identifying variables (approximate percentage of records)**

- baby's surname
- baby's first given name
- baby's sex
- baby's year, month, and day of birth
- father's surname
- father's first given name
- mother's first given name
- parents' place of residence, province or country
- parents' place of residence, city
- postal code

* The data are not organized to assess percentage of records at this time.

Access

Policy	•	none at present
Procedure	•	would have to obtain membership approval
Type of access	•	negotiated
Resources available	•	none at present
Costs	•	to be negotiated
Contact person	•	Ms Donna Launslager (519) 884-1929



Prince Edward Island Perinatal Data Base

PEI Reproductive Care Program Inc.
PEI Medical Society
559 North River Road
Charlottetown, Prince Edward Island
C1E 1J7

General Characteristics

Purpose	• to provide information/statistics on perinatal morbidity/mortality, lifestyle factors, and intervention programs on outcome data, such as length of pregnancy and birthweight
Relevant content	• detailed information not known at this time
Target population	• all women who become pregnant in the province of PEI
Coverage	• no known bias
	• estimated proportion of the target population included will be 100%
Data collection	• ongoing process, which will be updated regularly, probably monthly
Time period	• data will be available for 1987 to the present, with an unlimited retention period
Size	• approximately 2 000 records will be added each year
Unit of analysis	• pregnancies (mothers will have an individual ID)

Technical Characteristics

Data storage	• in machine-readable form not finalized at this time; it is expected to be as raw data, and/or in a software-defined data base

Previous record linkage
- none (data base is in preliminary stages)

*Identifying variables (approximate percentage of records)**

- surname
- first given name
- sex
- year, month, and day of birth
- own place of residence, province or country
- own place of residence, city
- postal code
- social insurance number
- health insurance number
- unique identifier

* The data base is just being set up and detailed information on identifiers is not known at this time.

Access

Policy
- policy and procedure yet to be established

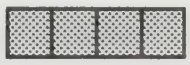
Procedure
- not yet specified

Type of access
- not yet specified

Resources available
- unknown at this time

Costs
- unknown at this time

Contact person
- Frances L. Wertman, Coordinator (902) 368-2759



Saskatchewan Cancer Registry

Saskatchewan Cancer Foundation
Suite 400, 2631 - 28th Avenue
Regina, Saskatchewan
S4S 6X3

General Characteristics

Purpose	• collected under the Saskatchewan Cancer Foundation Act to provide cancer incidence data
Relevant content	• demographics, cancer diagnoses (ICD-9 codes 140-239, neoplasms and some benign neoplasms), date of diagnosis, method of diagnosis, histology, behaviour of the neoplasms, metastases at diagnosis, summary treatment at diagnosis, pathology number, and date of last follow-up, etc.
Target population	• Saskatchewan population diagnosed as having cancer; no exclusions
Coverage	• no known bias • estimated proportion of the target population included is 100%
Data collection	• ongoing process, which is updated continuously through the two cancer treatment centres
Time period	• data available for 1967 to the present, with an unlimited retention period
Size	• approximately 4 000 new invasive cancers a year, plus 2 000 non-melanoma skin cancer and in situ cases
Unit of analysis	• individual cases records

Technical Characteristics

Data storage
- in machine-readable form as raw data since 1967

Previous record linkage
- has been linked to the Saskatchewan Health Data Bases and to Labour Canada data bases

Identifying variables (approximate percentage of records)

- surname (100%)
- alternate surname ever used (16%)
- first given name (98%)
- first initial (98%)
- second given name (unknown, high)
- second initial (unknown, high)
- usual name or nickname (small)
- sex (100%)
- marital status (50%)
- year, month, and day of birth (100% on year/month, partial on day, 83% on all three)
- own place of residence, province or country (100%)
- own place of residence, city (93%)
- last known year alive (95%)
- year, month, and day of death (95% of applicable)
- place of death, province or country (36% of applicable)
- death registration number (36% of applicable)
- health services number (95%)

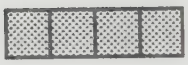
Access

Policy
- established policy and procedure

Procedure
- detailed requests to be submitted in writing, and are subject to approval by the Saskatchewan Cancer Foundation

Type of access
- through Saskatchewan Cancer Foundation

Resources available	• software, machine time, and experienced personnel (both data/project consultants and programmer analysts)
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Ms Diane Robson, Director of Data Services (306) 585-1872



Saskatchewan Health Data Bases

Pharmacoepidemiology Unit
Saskatchewan Laboratory and Disease Control Services Branch
3211 Albert Street
Regina, Saskatchewan
S4S 5W6

General Characteristics

Purpose

- collected for program administration and used for program management and research

Relevant content

- demographic information, outpatient prescription drug records, hospital discharge information, physician services claims, mental health services, institutional long-term care services, home care services, vital statistics records (birth and death registrations), and some other information (e.g., some alcohol and drug abuse treatment services, information on insured dental services, etc.)

Target population

- Saskatchewan population eligible for Saskatchewan Health benefits (1 010 526 as of 30 June 1991); excludes about 6% of the population whose health care is federally funded (e.g., members of the RCMP, the Canadian Forces, and inmates of federal penitentiaries); registered Indians are excluded from the Saskatchewan Drug Plan because their costs are paid by the federal government

Coverage

- no known bias
- estimated proportion of the target population included is 94%

Data collection

- ongoing process, updated regularly

Time period

- data are available on:

  demographic information: for 1962 to present
  prescription drug records: for 1975 to present
  hospital discharge records: for 1970 to present
  physician services records: for 1971 to present

  with an unlimited retention period

Size

- added in 1989-1990
  - 5.4 million prescription records
  - 223 600 hospital discharge records
  - 13.8 million physician services records

Unit of analysis

- individual or events (services)

Technical Characteristics

Data storage

- in machine-readable form as raw data

Previous record linkage

- different data bases have been used individually or linked for assorted research (references available)

Identifying variables (approximate percentage of records)

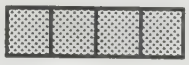
- surname* (100%)
- first given name* (100%)
- first initial* (100%)
- sex (100%)
- marital status* (100%)
- year and month of birth** (100%)
- year, month, and day of death (100%, where applicable)
- health services number (100%, except historical vital statistics)

* These identifiers do not reside in all data bases but can be obtained through linkage with the demographic data base using the health services number.

** Day of birth available only if vital statistics birth registration information used.

Access

Policy	• established policy and procedure
Procedure	• detailed requests to be submitted in writing, and are subject to approval by Saskatchewan Health
Type of access	• indirect through Saskatchewan Health
Resources available	• software (primarily COBOL and SAS), machine time, and experienced personnel (data/project consultants and programmer analysts)
Costs	• quote prepared for each request on a cost-recovery basis
Contact person	• Dr. Linda Strand, Executive Director (306) 787-3129



Quebec Vital Statistics (Statistiques démographics [Québec])

Ministère de la Santé et des Services sociaux
1279, boul. Charest ouest
Québec (Québec)
G1N 4K7

General Characteristics

Purpose
- to gather and analyze demographic events, vital statistics

Relevant content
- birth and stillbirth statistics such as date and place of birth, marital status of mother, age and ethnicity of parents, duration of pregnancy, birthweight, kind of birth (twins etc.), birth order, immediate cause of stillbirth, antecedent cause, autopsy, point of death, etc.

Target population
- population of Quebec, all births, stillbirths, and deaths in Quebec and for all Quebec residents

Coverage
- no known bias
- estimated proportion of the target population included is 99%

Data collection
- ongoing process, continuously updated

Time period
- data is available for 1975-1990 in machine-readable form, with an unlimited retention period

Size
- approximately: 90 000 births per year
  425 stillbirths per year
  50 000 deaths per year

Unit of analysis
- individual

Technical Characteristics

Data storage
- in machine-readable form as raw data (flat file), in a software defined data base (dBase), or to client specifications

Previous record linkage
- unknown (sensitive issue)

*Identifying variables (approximate percentage of records)**

- surname
- first given name
- second given name
- sex
- marital status
- year, month, and day of birth
- birth province or country
- father's surname
- father's first given name
- father's first initial
- father's second initial
- father's year, month, and day of birth
- father's birth province or country
- mother's maiden name
- mother's first given name
- mother's first initial
- mother's second initial
- mother's year, month, and day of birth
- mother's birth province or country
- own place of residence, province or country
- own place of residence, city
- postal code (first three digits)

* The presence of each identifier and proportion of records varies by file, therefore it is not indicated here.

Access

Policy
- established policy and procedure

Procedure
- detailed requests to be submitted in writing, and may be subject to the approval of the Information Access Commission

Type of access
- negotiated

Resources available	• software (data base), machine time, and experienced personnel
Costs	• have a fee schedule
Contact person	• Lorraine Nadeau (418) 643-6209

Appendix 1: List of Relevant Data Bases Explored

Data Base	Contact	Telephone
Saskatchewan Health Data Base	Linda Strand, Executive Director Pharmacoepidemiology Unit Saskatchewan Laboratory and Disease Control Services Branch 3211 Albert Street Regina, Saskatchewan S4S 5W6	(306) 787-7625
British Columbia Drug Data Base	Executive Director, Pharmacare Bob Harth for John Greschner Executive Director, Pharmacare 3-1 1515 Blanshard Street Victoria, British Columbia V8W 3C8	(604) 356-7654 (604) 387-2277
Ontario Health Survey (OHS) 1990	David Bogart, Director Information Resources Branch Ontario Ministry of Health 15 Overlea Boulevard, 2nd Floor Toronto, Ontario M4H 1A9	(416) 327-7610
Quebec Health Survey (Enquête Santé [Québec]) 1987	Aline Émonde Directeur Santé Québec 600 ouest boul. René Levesque 10ième étage Montreal, Quebec H3B 1N4	(514) 873-4749
Health Promotion Survey (CHS) 1990	Reg Warren Health Promotion Studies Unit Health and Welfare Canada	(613) 954-8835

Data Base	Contact	Telephone
Canada Health Survey (CHS) 1978-79	Wayne Millar, Analyst Health Status Section Canadian Centre for Health Information Statistics Canada R.H. Coats Building, 18th Floor Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-1631
Canada Fitness Survey 1981 and Follow-Up 1988	Cora Craig, Executive Director Canadian Fitness and Lifestyle Research Institute Suite 313, 1600 James Naismith Gloucester, Ontario K1B 5N4	(613) 748-5791
General Social Survey 1985 (Cycles 5 and 6, 1990, 1991) (Pretest) 1990, 1991	Ed Praught General Social Survey Statistics Canada R.H. Coats Building Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-9180
Census of Canada	Russell Wilkins Occupational and Environmental Health CCHI Ottawa, Ontario K1A 0T6	(613) 951-1633
In-Vitro Fertilization (IVF) Registry	Dr. Arthur Leader Director, IVF Program Canadian Voluntary Regulatory Association Suite 570, Parkdale Clinic Ottawa Civic Hospital 1053 Carling Avenue Ottawa, Ontario K1Y 4E9	(613) 761-4427

Data Base	Contact	Telephone
Canadian Infertility Therapy Evaluation Study (CITES) (Collins)	Dr. J.A. Collins Peter Tihanyi Deptartment of Obstetrics and Gynaecology McMaster University Medical Centre 1200 Main Street West, Room 4D9 Hamilton, Ontario L8N 3Z5	(905) 525-9140 ext. 22566
RCNRT Patient Survey	Janet Hatcher Roberts RCNRT	(613) 954-9999
Provincial Physician Billings - Saskatchewan	Winanne Downey (see top of previous page) facilitates linkage of drug data bases with all other provincial health data bases	(306) 787-7625
Provincial Physician Billings - Manitoba	Guenter Bormann Manitoba Health Management Information Systems Box 925 Winnipeg, Manitoba R3C 2T6	(604) 387-8001
Provincial Physician Billings - Ontario	David Bogart, Director Information Resources Branch Ontario Ministry of Health 15 Overlea Boulevard Toronto, Ontario M4H 1A9	(416) 327-4610
Provincial Physician Billings - British Columbia	Peter Durant Michael Shay Claims Branch, MOH 3rd Floor, 1515 Blanshard Street Victoria, British Columbia V8W 3C8	(604) 387-8001 (604) 387-8076
Hospital Medical Records Institute Data Bases (HMRI) (hospital separations)	Chris Helyar, Vice President Hospital Medical Records Institute 250 Ferrand Drive, 5th Floor P.O. Box 3900 Don Mills, Ontario M3C 2T9	(416) 429-1953

Data Base	Contact	Telephone
Med-Echo (hospital separations)	Pierre Ferland Research Agent, DHC Hôpital Sainte Croix 570 Heriot Drummondville, Quebec J2B 1C1	(819) 477-6221
Statistics Canada - Vital Statistics - Birth Certificate - Death Certificate - Physician's Notification of Birth	Dr. Jane Gentleman Chief, Vital Statistics Canadian Centre for Health Information R.H. Coats Building 18th Floor, Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-8553
British Columbia Vital Statistics Data Definition Survey (and other surveys)	Dr. R.J. Dandefer, Executive Director Mark Collison Manager, Corporate Affairs Division of Vital Statistics Ministry of Health 818 Fort Street, 3rd Floor Victoria, British Columbia V8W 1H8	(604) 387-4807 (604) 387-4832
Quebec Vital Statistics (Statistiques démographiques [Québec])	Lorraine Nadeau Ministère de la Santé et des Services sociaux 1879, boul. Charest ouest Quebec, Quebec G1N 4K7	(418) 643-6209
Canadian Mortality Data Base (CMDB)	Martha Fair, Chief Occupational and Environmental Health Research Section Station 18Q R.H. Coats Building, 18th Floor Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-1734

Data Base	Contact	Telephone
Canadian Cancer Data Base (CCDB)	Martha Fair, Chief Occupational and Environmental Health Research Section Station 18Q Canadian Centre for Health Statistics Statistics Canada R.H. Coats Building, 18th Floor Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-1734 (613) 951-1769
Quebec Cancer Registry (Déclaration des tumeurs [Quebec])	Lorraine Nadeau Ministère de la Santé et des Services sociaux 1879 boul. Charest ouest Quebec, Quebec G1N 4K7	(418) 643-6209
Canadian Birth Data Base (CBDB)	Martha Fair, Chief Occupational and Environmental Health Research Section Station 18Q Canadian Centre for Health Information Statistics Canada R.H. Coats Building, 18th Floor Tunney's Pasture Ottawa, Ontario K1A 0T6	(613) 951-1760
Health Activity and Limitation Survey	Adele Furrie Jean Pierre Moray Marie Patry Disability Database Program Jean Talon Building 9th Floor, Section C8 Ottawa, Ontario K1A 0T6	(613) 951-4414 (613) 951-4532
Easter Seal Client Registry	Asha Nambyarooran Registry Coordinator Easter Seal Society 250 Ferrand Drive, Suite 200 Don Mills, Ontario M3C 3P2	(416) 421-8377

Data Base	Contact	Telephone
British Columbia Cancer Registry	Dr. Mary McBride British Columbia Cancer Agency Division of Epidemiology 600 West 10th Avenue Vancouver, British Columbia V5Z 4E6	(604) 877-6000 ext. 3060
Ontario Cancer Registry (OCR)	Darlene Dale Manager of Operations Cancer Registration Unit Ontario Cancer Treatment and Research Foundation 7 Overlea Boulevard Toronto, Ontario M4H 1A8	(416) 423-4240 Ext. 248
Nova Scotia Perinatal Data Base	Dr. Becky Attenborough, Head Dr. Linda Dodds, Epidemiologist Nova Scotia Reproductive Care Program 5821 University Avenue Halifax, Nova Scotia B3H 1W3	(902) 420-6798
British Columbia Perinatal Data Base	Dr. Robert Armstrong Department of Pediatrics Sunny Hill Hospital 3644 Flocan Street Vancouver, British Columbia V5M 3E8	(604) 433-4449
Prince Edward Island Perinatal Data Base	Frances L. Wertman, Coordinator PEI Reproductive Care Program Inc. PEI Medical Society 559 North River Road Charlottetown, Prince Edward Island C1E 1J7	(902) 368-2759
Comprehensive Integrated Perinatal Data Base and the Health and Safety Data Base	Dr. Louise Denhez Community Health Department Maisoneuve Rosemont 5565 Sherbrooke Street East, Suite 470 Montreal, Quebec H1N 1A2	(514) 252-3973

Data Base	Contact	Telephone
Hamilton-Wentworth Regional Perinatal Program Data Base	Dr. Sarot Saigal McMaster University Medical Centre - Pediatrics Room 3 - C20 1200 Main Street West Hamilton, Ontario L8N 4K1	(905) 521-2100 ext. 6959
Chedoke-McMaster Hospitals Labour and Delivery Data Base	Dr. P.T. Mohide Dept. of Obstetrics and Gynaecology Chedoke-McMaster Hospital 1200 Main Street West, Room 4D10 Hamilton, Ontario L8N 3Z5	(905) 521-2100 ext. 6245
Canadian Congenital Anomalies Surveillance System (CCASS)	Dr. Greg Sherman Birth Defect Section Laboratory Centre for Disease Control Room 28C, Tunney's Pasture Ottawa, Ontario K1A 0LC	(613) 957-0853
British Columbia Health Surveillance Registry	Dr. Sam Sheps Health Care and Epidemiology, UBC 5804 Fairview Avenue Vancouver, British Columbia V6T 1Z3	(604) 822-2772
Ontario Child Health Study, (1983) and Follow-Up (1987)	Dr. Michael Boyle Department of Psychiatry McMaster University 106A Melville Street Dundas, Ontario L9H 2A3	(416) 521-2100 ext. 7359
Parents of Multiple Births Association of Canada, Impact of the Family Survey 1991 (Pretest)	Ms Donna Launslager Director of Multiple Services 4918 Highway #7 East Unit 12A, Suite 161 Markham, Ontario L3R 1N1	(519) 884-1929

Data Base	Contact	Telephone
Ontario Reportable Diseases Information System (RDIS)	Dr. Richard Schabas Chief Medical Officer and Executive Director Public Health Branch Ministry of Health 15 Overlea Boulevard, 5th Floor Toronto, Ontario M4H 1A9	(416) 327-7433
Manitoba Chlamidia Data Base	Dr. P.H. Orr Professor Department of Medical Microbiology University of Manitoba Basic Sciences Building 730 William Avenue, Room 503 Winnipeg, Manitoba R3E 0W3	(204) 788-6357
Ontario Health Insurance Plan (OHIP) Detailed Claims File	David Bogart, Director Information Resources Branch Ontario Ministry of Health 15 Overlea Boulevard Toronto, Ontario M4H 1A9	(416) 327-7610

Appendix 2: Covering Letter and Child Health Study Questionnaire

Dear

Thank you for agreeing to participate in the Child Health Study. As discussed, we are conducting a feasibility study on record linkage for the Royal Commission on New Reproductive Technologies. The final report will include a catalogue of exposure and outcome data bases relevant to the Commission's mandate. Such a study could facilitate further study and assessment of the consequences for children of certain treatments and exposures.

Attached is the questionnaire designed to solicit information from guardians of relevant data bases on factors which influence the possibility of record linkage. We would like you to complete the questionnaire for the Regional Perinatal Program data base by Friday, 10 April, if possible, given the very tight deadline the Commission has for this project. You may return the questionnaire by fax [(613) 594-8705] or by the pre-addressed and pre-paid courier pack, whichever is most convenient.

In addition to the completed questionnaire, we would appreciate any related data base materials (e.g., questionnaires used, coding manuals) that would help us to describe and better understand your data base. Moreover, if you know of any other data bases that you think may be relevant to the project, we would like to know of those as well. This material could be sent later than the completion of the questionnaire, if that is more convenient.

Should you have any questions about our request or the questionnaire, please call me or Christine Davis at (613) 594-9589 or (613) 521-8052. For further information about the study you may call Janet Hatcher Roberts, Deputy Director of the Evaluation and Research Program at the Commission [(613) 954-9999]. Again many thanks for your assistance with this project.

Yours sincerely,

Darlene Flett, CMC
Project Manager

Child Health Study Questionnaire
Royal Commission on New Reproductive Technologies

The purpose of this questionnaire is to gather information that will help us assess the record linkage possibilities of relevant Canadian data bases for the Child Health Study being conducted by the Royal Commission on New Reproductive Technologies. Your assistance is greatly appreciated. Please circle the appropriate answer or print your response in the space provided. If you have any questions, please call Darlene Flett, the project manager, or Christine Davis at (613) 594-9589 or (613) 521-8052. When you have completed the questionnaire, please return it to us in the pre-addressed and pre-paid courier pack or by fax (613) 594-8705. Thank you.

First, we would like to ask you a few general questions about the data base.

1. Please write the full formal name of the data base in the space provided below.

   _____
   _____
   _____

   a) Has this data base been known by any other names?

      1 Yes ... Please list

      _____
      _____
      _____

      2 No

2. Who owns and has jurisdiction over the use of this data?

   _____

3. Where is the data base physically located? Please indicate city and province.

   _____ _____
   province city

4. Briefly, describe the purpose for which this data base was designed.

_____

_____

_____

5. What is the target population for the data base? Please indicate geographical area, demographic characteristics, gender, etc.

_____

_____

_____

a) Are any groups excluded from the sample such as persons residing in institutions or living on reservations etc.?

1 yes ... please describe

_____

_____

2 no ...

6. Are the data collected for a sample?

1 yes

2 no ... (GO TO Q7)

a) If yes, approximately what proportion of the population was sampled?

_____

b) Is weighting required to make the sample representative?

1 yes

2 no

7. What is your overall response rate? _____ %

8. Are there any known biases in the coverage of the population?

1 yes ... Please explain

_____

_____

9. In general, what proportion of the target population is included in the final data base?

_____ %

10. Would you say these data are ... (PLEASE CIRCLE ALL THAT APPLY)

1 a one time, cross-sectional survey

2 a longitudinal survey that follows the same group of respondents over a period of time

3 a repeated survey with different respondents each time, such as an annual study to monitor the public awareness of a health promotion program

4 or an ongoing data collection process which is updated as each new event occurs

IF A ONE TIME SURVEY, PLEASE GO TO Q12.

11. What is the frequency of collection? Is it ...

1 variable ... (GO TO Q12)

2 at regular intervals

a) If at regular intervals, would this be ...

1 weekly

2 monthly

3 semi-annual

4 annual

5 some other interval ... Please specify

_____

b) Approximately how many records are added each time?

_____

c) Is there a planned completion date, for example a 5 year study ending in 1993?

1 yes ... When will that be? _____ _____

2 no

12. Is there a limited period over which the data will be retained, for example, 5 years?

1 yes ... Please specify

_____

2 no

13. For what time period are the data presently available?

From _____ to _____

14. Approximately, what is the size of the data base?

_____ records per year, or

_____ records in total

The next few questions deal with technical characteristics of the data base which are important in assessing the feasibility of record linkage.

15. How is this data base stored?

1 in machine readable form as raw data (i.e., ASCII)

2 in a software defined data base (i.e., a SAS or DBase data base)

3 in some other form ... Please describe

_____

16. Is the unit of analysis ...

1 individual (i.e., a case history, with one record per individual)

2 family (i.e., a family history, family registration)

3 event (i.e., Dr. visits, with varying numbers of records per individual)

4 or something else (i.e., number of procedures performed). Please explain ...

_____

_____

17. Has this data base been linked to other data bases?

1 yes

2 no ... (GO TO Q18)

a) If yes, which data bases have been linked? Please list.

_____

_____

_____

The question below concerns the presence of identifying variables which could be used to link records across data bases. We realize that each data base has necessary confidentiality concerns associated with these variables. At this time we are not asking about the availability of this information per se, rather we are trying to assess the technical possibility of linkage.

18. For each identifying variable listed could you please check in the appropriate column if it is retained in machine readable or some other form (i.e., a list), and note approximately what proportion of the records in the data base contain information for this variable. For example, the data base may have a field for nickname, however only 10% of the records had individuals with nicknames.

Identifying Variable	Retained in		Percentage of records in which variable is found
	machine readable form	some other form	
1. surname			
2. alternate surname ever used			
3. first given name			
4. first initial			
5. second given name			
6. second initial			
7. usual name or nickname			
8. sex			
9. marital status			
10. year of birth			
11. month of birth			
12. day of birth			
13. birth province or country			
14. birth city or place			
15. father's surname			
16. father's first given name			
17. father's first initial			
18. father's second name			
19. father's second initial			

Identifying Variable	Retained in		Percentage of records in which variable is found
	machine readable form	some other form	
20. father's birth province or country			
21. mother's maiden name			
22. mother's first given name			
23. mother's first initial			
24. mother's second initial			
25. mother's second given name			
26. mother's birth province or country			
27. own place of residence (province or country)			
28. own place of residence (city/town)			
29. postal code			
30. last known year alive			
31. year of death			
32. month of death			
33. day of death			
34. place of death (province or country)			

Identifying Variable	Retained in		Percentage of records in which variable is found
	machine readable form	some other form	
35. place of death (city/town)			
36. social insurance number			
37. death registration number			
38. health insurance number			
39. other identifying numbers, please specify			
40. other identifying variables, please specify			

19. Is this data base sorted by any of the above identifying variables?

    1 yes ... Which?

    _____

    _____

    2 no

The last few questions deal with requirements for access to this data base.

20. Have you established a policy or procedure for access to this data base for record linkage?

    1 yes

    2 no ... Is there any particular reason?

_____

_____

21. Briefly describe what the application process would involve if someone wished to link the records in this data base to another data base.

_____

_____

_____

22. Are there specific restrictions on who would be eligible to apply for a record linkage?

1 yes

2 no ... (GO TO Q23)

a) If yes, please explain

_____

_____

23. Would an applicant have direct or indirect access to the data base?

1 direct (i.e., could link at applicant's site)

2 indirect (requests would be handled by you)

3 negotiated

4 no access given for record linkage ... (GO TO Q27)

24. Do you have the facilities (software, machine time and personnel) available to do record linkages at your site?

	yes	**no**
a) software, specify _____	1	2
b) machine time	1	2
c) experienced personnel	1	2

25. With regard to the costs an applicant could expect when linking to your data base, do you ...

1 have a fee schedule

2 prepare a quote for each request

3 or something else? Please explain ...

_____

_____

26. Please briefly describe any restrictions on the use of a linked file and the information released?

_____

_____

27. Do you anticipate any major changes in policy concerning record linkage with this data base in the next 5 years?

1 yes ... please explain

_____

_____

2 no

28. Attached is the initial list of data bases we have identified as relevant for this project. Are you aware of any other data bases which could be of interest in the study of risks to fertility and new reproductive technologies and their outcomes for the child? If so, could you please list them below and if possible give us the name and telephone number of a contact person.

Data Base Name	Contact	Phone

29. Finally, would you like to make any further comments?

_____

_____

_____

THANK YOU FOR YOUR ASSISTANCE

Initial List of Relevant Data Bases

1. Saskatchewan Health Data Base
2. British Columbia Drug Data Base
3. Ontario Health Survey (OHS) 1990
4. Health Promotion Survey 1990
5. Canada Health Survey (CHS) 1978-79
6. Canada Fitness Survey and Follow-Up 1988
7. General Social Survey (Cycles 5 and 6, 1985, 1991)
8. Census of Canada
9. In Vitro Fertilization (IVF) Registry
10. Canadian Infertility Therapy Evaluation Study (CITES) (Collins)
11. Royal Commission on New Reproductive Technologies (Patient Survey)
12. Provincial Physician Billings
    - Saskatchewan
    - Manitoba
    - Ontario
    - British Columbia
13. Hospital (Medical Records Institute (HMRI) Data Bases Hospital Separations)
14. Statistics Canada Vital Statistics
    - Birth Certificate
    - Death Certificate
    - Physician's Notification of Birth
15. Canadian Cancer Data Bases (CCDB)
16. Canadian Mortality Data Base (CMDB)
17. Health Activity and Limitation Survey (HALS)
18. Ontario Cancer Registry (OCR)

19. Nova Scotia Perinatal Data Base

20. British Columbia Perinatal Data Base

21. Congenital Anomalies Surveillance System (CCASS)

22. British Columbia Health Surveillance Registry

23. Easter Seal Client Registry

24. Ontario Child Health Study (1983 and Foll-Up 1987)

25. Parents of Multiple Births Association (POMBA) Registry

Notes

1. Canada, Royal Commission on New Reproductive Technologies, *What We Heard, Issues and Questions Raised During the Public Hearings* (Ottawa: RCNRT, 1991).

2. For examples of Canadian studies of risk factors and reproductive outcome involving record linkage see: H.B. Newcombe, "Record Linking: The Design of Efficient Systems for Linking Records into Individual and Family Histories," *American Journal of Human Genetics* 19 (1987): 335-59; A.F. Olshan, K. Teschke, and P.A. Baird, "Birth Defects Among Offspring of Firemen," *American Journal of Epidemiology* 131 (1990): 312-21; G.M. Anderson, "An Analysis of Temporal and Regional Trends in the Use of Prenatal Ultrasound," report submitted to the Royal Commission on New Reproductive Technologies, 1992.

3. Canada, National Health Information Council, *Health Information for Canada 1991: Report of the National Task Force on Health Information* (Ottawa: National Health Information Council, 1992), 3.

4. H. Shannon, "Summary of First Half of Discussion Groups 1 and 2 — Statistical Methodology and Computer Hardware/Software," in *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*, ed. G.R. Howe and R.A. Spasoff. (Toronto: University of Toronto Press, 1986).

5. For a historical overview of the development of probabilistic record linkage in Canada see, for example: F. Scheuren, "Methodological Issues on Linkage of Multiple Data Bases," in *Health of an Aging America: Issues on Data for Policy Analysis* (Hyattsville: U.S. Department of Health and Human Services, 1988); W.E. Winkler, "The Interaction of Record Linkage Practice and Theory," in *Canadian Epidemiology Research Conference — 1989, Proceedings of the Record Linkage Sessions and Workshop Ottawa, Ontario, August 30-31, 1989* (Ottawa: Statistics Canada, Canadian Centre for Health Information, 1990).

6. H.B. Newcombe et al., "Automatic Linkage of Vital Records," *Science* 130 (1959): 954-59.

7. Previously known as the Generalized Iterative Record Linkage System (GIRLS), and as CANLINK.

8. G. Wagner and H.B. Newcombe, "Record Linkage: Its Methodology and Application in Medical Data Processing," *Methods of Information in Medicine* 9 (1970): 121-38.

9. M. Smith, "Future Needs and Directions for Computerizing Record Linkage in Health Research in Canada: Future Study Plans," *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*, ed. G.R. Howe and R.A. Spasoff (Toronto: University of Toronto Press, 1986).

10. Examples of discussions of the advantages and disadvantages of record linkage can be found in: H. Johansen "Record Linkage of National Surveys: The Nutrition Canada Experience," in *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*, ed. G.R. Howe and R.A. Spasoff (Toronto: University of Toronto Press, 1986); J. Silins, "Incidence Studies and Registries: An Overview," in *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*, ed. G.R. Howe and R.A. Spasoff (Toronto: University of Toronto Press, 1986); Nova Scotia Saskatchewan Cardiovascular Epidemiology Study Group, "The Nova Scotia Saskatchewan Heart Study," in *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*, ed. G.R. Howe and R.A. Spasoff (Toronto: University of Toronto Press, 1986); Smith, "Future Needs and Directions for Computerizing Record Linkage."

11. National Health Information Council, Health Information for Canada 1991, 5.

12. C.H. Hennekens and J.E. Buring, *Epidemiology in Medicine* (Boston: Little, Brown, 1987).

13. Royal Commission on New Reproductive Technologies, *What We Heard.*

14. Scheuren, "Methodological Issues on Linkage of Multiple Data Bases."

15. P. Lalonde, "Preprocessing: Spell and Sex Code Check," in *Canadian Epidemiology Research Conference - 1989, Proceedings of the Record Linkage Sessions and Workshop, Otttawa, Ontario, August 30-31, 1989* (Ottawa: Statistics Canada, Canadian Centre for Health Information, 1990).

16. Shannon, "Summary of First Half of Discussion Groups 1 and 2."

17. *Canadian Mortality Data Base; Canadian Cancer Data Base* (Ottawa: Statistics Canada, Canadian Centre for Health Information, Occupational and Environmental Health Research Section, 1989).

18. Although two separate studies were commissioned, the two worked in close contact, sharing information on potential data bases, the questionnaire and data collection methodology developed by The Flett Consulting Group Inc., and the findings.

19. Medical Research Council of Canada, *Health Research Uses of Record Linkage in Canada: A Report to the Ad Hoc Committee on the Implications of Record Linkage for Health-Related Research, Medical Research Council of Canada* (Ottawa: MRC, 1968).

20. It was not part of the project's mandate to assess the quality of the data. The data bases were selected for this project because they have relevant content. This

is not an exhaustive list. The assessment of quality is largely dependent on the particular research being conducted and the level of detail required by the researchers. We have suggested some data sets worthy of investigation and supplied sufficient information for the researcher to contact the data base guardians, leaving the determination of quality to the individual researcher.

21. A list of minimal personal identifiers required for record linkage was obtained in a key informant interview with Ms. Martha Fair (nee Smith), Occupational and Environmental Health Research Section, Canadian Centre for Health Information, Statistics Canada.

22. National Health Information Council, *Health Information for Canada 1991.*

23. M. Carpenter and M.E. Fair "A Standard Data Collection Package for Medical Follow-Up Studies," *Health Reports* 2 (1990): 157-73.

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Canada. Royal Commission on New Reproductive Technologies. *What We Heard, Issues and Questions Raised During the Public Hearings*, Ottawa: RCNRT, 1991.

Canada. Statistics Canada. Occupational and Environmental Health Research Section. *The Canadian Cancer Data Base Availability of Information.* Ottawa: Statistics Canada, Canadian Centre for Health Information, 1991.

Canadian Mortality Data Base; Canadian Cancer Data Base. Ottawa: Statistics Canada, Canadian Centre for Health Information, Occupational and Environmental Health Research Section, 1989.

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"Data Collection Package." Ottawa: Statistics Canada, Canadian Centre for Health Information, 1990.

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—. "Radiation Studies in Canada: The National Files and Facilities Needed." In *Workshop Symposium on Radiation Protection; Past and Future*, 20-22 March,

held at Atomic Energy of Canada Limited, Chalk River Nuclear Laboratories, Chalk River, Ontario, Canada, 1989.

—. "Record Linkage: The Canadian Experience." Paper presented at *New Horizons in Health Information: A Forum to Discuss Issues and Technology*. Albany: 1989.

—. *Studies and References Relating to the Uses of the Canadian Mortality Data Base*. Ottawa: Statistics Canada, Canadian Centre for Health Information, Occupational and Environmental Health Research Section, 1989.

Fair, M.E., M. Carpenter, and P. Lalonde. "Long Term Medical Follow-Up Studies." Ottawa: Statistics Canada, Occupational and Environmental Health Research Section, 1991.

Flett Consulting Group Inc. "Review of Government Data Bases and Surveys." Report submitted to the Royal Commission on New Reproductive Technologies, 1990.

Hennekens, C.H., and J.E. Buring. *Epidemiology in Medicine*. Boston: Little, Brown, 1987.

Howe, G.R., and R.A. Spasoff, eds. *Proceedings of the Workshop on Computerized Record Linkage in Health Research, Ottawa, May 21-23, 1986*. Toronto: University of Toronto Press, 1986.

Index of federal information banks. Ottawa: Treasury Board Canada, 1980.

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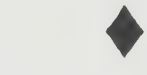
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11

Infertility Treatment — Epidemiology, Efficacy, Outcomes and Direct Costs: A Feasibility Study, Saskatchewan 1978-1990

Carl D'Arcy, Nigel S.B. Rawson, and Lindsay Edouard



Executive Summary

The authors propose to carry out a study of infertility treatment in Saskatchewan for the period 1 January 1978 to 31 December 1990. It would provide basic epidemiologic data on medically assisted human reproduction as well as data on the clients and practitioners involved, relative efficacy of procedures, factors associated with "successful" and "unsuccessful" outcomes, negative health outcomes, direct costs, and relative economic costs of successful births brought about through assisted human reproduction.

Its basic design would be that of a large non-concurrent prospective exposed cohort and comparison group study. We would identify an "infertile" cohort, their partners, and offspring born subsequent to infertility treatment, and follow them through the data files of the Medical Care Insurance Branch, the Saskatchewan Prescription Drug Plan, the Hospital Services Branch, and the Saskatchewan Cancer Foundation searching for adverse health events. A 2× comparison group would be identified and followed for similar outcomes.

This paper was completed for the Royal Commission on New Reproductive Technologies in June 1992.

A range of data analysis methods would be employed. This is to be a population-based study.

The proposed study is unique in four ways:

1. the experience of a geographically defined population of approximately one million, rather than a group of clinic clients, would be studied;
2. a wide range of reproductive techniques would be assessed;
3. a wide range of linked health and vital statistics data files, provided by Saskatchewan's health care system, would be used; and
4. it would involve a long-range follow-up of subjects (up to 12 years).

The authors estimate a period of 15 to 18 months to the study's completion and the writing up of the study's results. A total budget of $206 057 is estimated for this study.

An additional, subsidiary study on the risk of infertility associated with the short- and long-term use of specific prescription drugs, using the same data set as the study outlined above and at essentially no extra cost is also proposed.

Introduction

There has been increasing awareness and concern expressed about infertility and its treatment. At the same time, there has been an increasing awareness of the need for more information about these practices and their medical and social implications. At the urging of various interest groups, these concerns gave rise in Canada in 1989 to the Royal Commission on New Reproductive Technology (RCNRT), chaired by Dr. Patricia Baird. The mandate of the Commission is essentially to:

- evaluate the context in which these technologies operate;
- gather information and data from diverse sources about technologies and practices around reproduction in Canada;
- assess the legal, social, and economic implications of their development and use; and
- make recommendations to Government.

There has also been growing recognition over the last several decades of the value potentially inherent in the health-related data that have accumulated as a result of the implementation of universal hospital and medical care programs in Canada and its provinces (Robertson 1973; Dunn 1946; Newcombe 1967; D'Arcy et al. 1976; Roos et al. 1979; Strand and West 1989; Young et al. 1991). There is rich epidemiologic, economic, and behavioural information relevant to health contained in these data sets.

This potential increases exponentially as we are able to link case information through time and across health sectors, and further link them with verifiable outcomes.

The current feasibility study marries the concerns about infertility with the information potential inherent in the linkable health care and vital statistics data files in the Province of Saskatchewan. It looks at the feasibility of a study using these data sources in providing information about:

- the extent and nature of assisted human reproduction;
- the rate at which assisted human reproduction produces live births;
- negative health outcomes associated with these procedures; and
- the direct costs to the health care system of providing medically assisted human reproduction services.

This exploratory study demonstrates the feasibility of linking data that are held in Saskatchewan. It outlines the steps necessary for such a research project, and some potential problems inherent in carrying it out.

Objectives

The primary objective of this report is to describe and examine the feasibility of, and methodology for, undertaking a record linkage study using Saskatchewan health care data files. Such a study would accomplish the following:

1. provide a basic descriptive epidemiology of assisted human reproduction. Specifically, it would answer these questions:
   (a) Who are the infertile who seek medical assistance for their infertility? What are their sociodemographic and medical characteristics?
   (b) What types of medical assistance are provided (e.g., drugs, surgical procedures)?
   (c) Who gets what type of assistance?
   (d) Who provides this assistance? What is their specialty, training, etc.?
2. estimate the relative success of assisted human reproduction in general, and specific types of reproductive assistance in particular, in yielding live births;
3. ex amine the negative health outcomes associated with various types of assisted human reproduction, looking at negative events

for (a) the mother (if treated), (b) the father (if treated), and (c) the child(ren):

(a) for mothers, it would estimate the relative occurrence of:
- continued infertility;
- neoplasms;
- spontaneous abortions;
- other specific health problems;
- overall morbidity; and
- mortality.

(b) for fathers, it would estimate the relative occurrence of continued infertility;

(c) for offspring resulting from these procedures, it would estimate the relative occurrence of:
- multiple births;
- low birthweight;
- stillbirths;
- birth defects;
- overall morbidity in the initial years of life (0 to 5 years);
- overall mortality in the initial years of life;
- longer-term health problems (5 to 12 years); and
- longer-term mortality.

4. estimate the occurrence of spontaneous treatment-independent pregnancies in the previously infertile; and

5. estimate the direct costs to the health care system of:

   (a) providing medical assistance for such couples; and

   (b) dealing with the negative health outcomes associated with medically assisted human reproduction.

The Problem

The literature on assisted human reproduction makes a distinction between sterility and infertility. *Sterility* is a complete inability to produce offspring. *Infertility* refers to a diminished capacity to produce offspring where the possibility of achieving conception is not completely ruled out. The usual clinical definition is the inability to conceive in the past 12 months (World Health Organization 1990, 1), although two years is also used because the likelihood of pregnancy in the second 12 months is significant.

The large majority of patients who attend specialist clinics for the investigation of infertility have never been pregnant, if female, or have never contributed to a conception, if male. They are said to be suffering from *primary infertility*. A smaller proportion of patients are those who have had,

or have contributed to, one or more previous pregnancies but are now not able to conceive or contribute to a conception. This is termed *secondary infertility.*

It is estimated that from 8% to 10% of couples experience some form of infertility during their reproductive life, although there are wide regional variations throughout the world (World Health Organization 1990, 2). These wide regional variations in infertility are not surprising, given that a significant amount of infertility may result from infectious disease.

Sources of infertility may reside in either the male or female partner, or in both. A 1985 multicentre World Health Organization (WHO) study of more than 10 000 infertile couples found a possible source of infertility in the male partner in 33% of cases. A possible source of infertility was found in the female partner in 25% of cases. Twenty percent of couples had a possible source of infertility in both the male and the female partner. In 15% of cases no discernible source of infertility could be found in either partner (World Health Organization 1990, 1, 8).

There is a variety of medical techniques available to assist conception. They range from surgical procedures to correct physical defects, to drugs that increase sperm count and viability, and drugs that stimulate ovulation, to artificial insemination, to more invasive interventions of *in vitro* fertilization (IVF) and embryo transfer, et cetera. Surrogate pregnancy, while medically mundane, is more socially dramatic. Several of these techniques allow genetic parentage to be separated from pregnancy. The considerable media attention given to the newer techniques has brought concern about reproductive choices and technology to the fore and has heightened medical, moral, legal, and social concerns about the issues they raise.

The success rates of various assisted human reproduction methods in bringing about live births are variable, and their overall success rate has not been impressive. Notwithstanding that lack of success, these reproductive assistance techniques have grown in use and demand.

A WHO report based on nationally available information to the end of 1988 estimates that worldwide success rates for IVF averaged 11.5% per treatment cycle, with the rate of live births estimated at 7.5%. They found 65% of IVF-induced pregnancies result in live births, with spontaneous abortions and ectopic pregnancies contributing most to early pregnancy loss.

In their review of IVF, Stanley and Webb (1990) note the lack of standardized reporting on IVF, inconsistencies in evaluating its outcomes, and the lack of comparative data on various techniques for evaluating the efficacy of IVF and other medically assisted human reproductive techniques. They also note the total lack of controlled studies of IVF — outcomes studies are largely retrospective studies from single clinics. In their view, there is a lack of long-term follow-up of IVF clients and births. From their review of the literature they report the percentage of live births per IVF treatment cycle as 8.5%, 8.4%, and 8.1% respectively for the United Kingdom, the United States, and Australia, according to national data.

However, they note that multiple births, pre-term births, age of women treated, social circumstances, and causes of infertility may confound a straightforward comparison of outcomes between countries, sites, and techniques.

Stanley and Webb also comment that randomized controlled trials of IVF are rare and badly needed. Longer-term follow-up of IVF patients is required. Linkage of IVF client data to birth defect registries and physician and hospital records, they note, would allow relatively inexpensive ascertainment of the long term morbidity in women and children that are associated with these procedures. Their review also notes the phenomenon of treatment-independent pregnancies in the previously infertile treatment groups.

Wagner and St. Clair (1989), in their review of six different studies of the efficacy of IVF treatment, report that from 7% to 28% of couples accepted for IVF treatment conceive naturally, either before treatment, while on the waiting list for treatment, or after treatment, within two years of the incident treatment episode. Using statistical modelling, Léridon and Spira (1984) found that for a group of sub-fertile couples unable to conceive for three years, the proportion spontaneously conceiving in the fourth year could be as high as 48%.

While there are acknowledged risks associated with IVF, there are also risks associated with other treatments for infertility. For example, negative health outcomes are associated with drugs used in ovulation induction. Ovulation induction involves stimulating the ovaries with drugs in order to encourage the maturation of multiple follicles. It is used on its own as a medical treatment for infertility if an ovulation defect is thought to be responsible. It is also used as a preparatory step in artificial insemination in some cases, and in IVF processes. Clomiphene citrate and human gonadotropins are two of the most frequently used drugs used for ovulation induction. By today's standards these drugs were never properly evaluated prior to their introduction into clinical practice. Today, some 30 years later, sound research on their adverse effects is still lacking (St. Clair Stephenson 1991, 7).

In reviewing the risks associated with ovulation induction, St. Clair Stephenson notes that both clomiphene and human gonadotropins are associated with multiple pregnancies and ovarian hyperstimulation. She calls for more carefully designed epidemiologic studies to determine the risks associated with exposure to these drugs.

From this brief review of the literature it is clearly evident that good basic epidemiologic data are needed regarding the occurrence of medically assisted human reproduction, the types of procedures involved and their level of use, characteristics of clients and service providers, efficacy of treatments, and health outcomes for both parents and children.

This lack of knowledge is even more acute for Canada.

The Proposed Study

The potential study described here would help to fill the knowledge gap documented above. It would provide basic epidemiologic data on medically assisted human reproduction, clients and practitioners involved, relative efficacy of procedures, factors associated with "successful" and "unsuccessful" outcomes, and negative health outcomes in a Canadian population.

The study would also be able to provide data on the direct costs to the health care system of these interventions and the relative economic costs of successful births brought about by assisted human reproduction. It is described in detail as a specific example of the kind of valuable study that could be performed by using a record linkage approach to already existing large data files. It is hoped the detailed description will encourage others to consider similar approaches to research on human reproduction.

The Choice of Study Site

Saskatchewan has been chosen as the site for the proposed study because of the availability of data on hospital, medical, and prescription drug use for the population at large.

During the period of the proposed study (1 January 1978 to 31 December 1990), Saskatchewan had a population of approximately one million people. In comparison with Canada as a whole, Saskatchewan is less urbanized. Some 60% of the provincial population reside in urban areas with a population of 5 000 or more; 37% are aged 40 years or more. The province also contains approximately 40% of the farmland in Canada. The economic base of the province is agriculture, though manufacturing and industry have increased in recent years. Mining, especially of potash and uranium, is important, and there is some oil and gas extraction.

The population has remained fairly stable at about one million for the last decade, even though, as in any geographically defined area, there is population flux, with some residents leaving and others entering.

Although the provincial population has hovered around one million, on the basis of the analysis of the population movement by the Health Information Registration File (HIRF), we estimate that 2 069 000 individuals were actually resident in Saskatchewan at some point during the period between June 1966 and May 1991.

Direct data from the Saskatchewan Prescription Drug Plan (in Table 1) show that in the year 1990, over 3 500 discrete patients were prescribed a drug that may have been used for infertility treatment.

On the basis of these data we conclude that the 13-year period of the proposed study would yield a sufficiently large number of subjects exposed to infertility treatment to allow meaningful analysis.

Table 1. Infertility Drug Therapy: 1990 Utilization Data

Drug patients	Number of prescriptions	Number of discrete patients (females)
Clomiphene citrate	3 000	975
Human menopausal gonadotrophin	188	90
Human chorionic gonadotrophin	195	109
Bromocriptine	4 222	2 072
Danazol®	1 317	390
Buserelin	17	11
Luprolide	309	86
Goserelin	-	-
Nafarelin®	-	-

Note: Bromocriptine and Danazol® are not covered under Exception Drug Status, as they are listed in the Saskatchewan Formulary. It is not possible to determine from our data base if these agents were prescribed for infertility or for other indications (e.g., Bromocriptine for Parkinson's disease, Danazol® for fibrocystic breast disease or endometriosis).

Patients receiving Buserelin, Luprolide, Goserelin, and Nafarelin® usually have a diagnosis of endometriosis. Endometriosis may result in infertility, but not all patients undergoing treatment for endometriosis do so in order to increase fertility. These drugs are also used for cancer treatment and are in such cases directly dispensed by the clinics of the Saskatchewan Cancer Foundation.

Source: Saskatchewan Department of Health, Prescription Drug Services Branch, 13 September 1991.

Uniqueness of the Proposed Study

There are four important ways in which the proposed study is unique:

1. the experience of a total geographic population of approximately 1 000 000 would be examined rather than the clients of one particular practice or clinic;
2. a wide range of reproductive techniques would be assessed;
3. Saskatchewan's health care system provides linkage of a wide range of health records and outcome information; and
4. follow-up of subjects would occur over a relatively long period — up to 12 years.

Study Design

The basic study design is that of a large non-concurrent prospective exposed cohort and comparison group study. It would use the Saskatchewan health care utilization data files as the source of data.

We propose to identify three groups in the population:

1. the cohort of *all women aged 25 to 49* in Saskatchewan who have received treatment for infertility and *all men aged 25 and older* also treated for infertility. They would be identified from the Saskatchewan Prescription Drug Plan, Hospital Services Branch, and the Medical Care Insurance Branch data files. Patients so identified would be the cohort of all those receiving infertility treatment during the period *1 January 1978 to 31 December 1990.* These data files would be further checked for the year 1977 to make sure that none of those selected in the 1978 cohort year had received any infertility treatment services in the previous 12 months. In essence there would be a "wash-out" period of at least 12 months before inclusion in the "infertile" cohort.

   (a) Cohort identification would be based *in part* on the use of the following prescription drugs, with the exception of the latter half of 1987 and the whole of 1988 (see Appendix 1 for details on this exception):
   - ovulation induction drugs: clomiphene citrate, bromocriptine, etc.;
   - ovulation suppression drugs: Danazol®, Gn-RH agonists;
   - luteal support therapy drugs: progestagens; and
   - estradiol.

   (b) Cohort identification would also be based on "infertility" diagnoses recorded on the payment claims records of physicians billing the provincial health plan for services rendered, and on hospital admissions for procedures relating to "infertility." (See Appendix 1 for a detailed description of criteria for cohort selection and file structure).

Although IVF is not provided directly in Saskatchewan, some of the costs (up to a specified maximum) of this treatment are covered for Saskatchewan residents who have the treatment provided out of province. An itemized bill is required. It is up to the patient to initiate the claim for reimbursement. The costs of drugs used in this treatment are covered by the Saskatchewan Prescription Drug Plan. Thus, data on IVF treatment for Saskatchewan residents are available.

2. partners — legal and common-law spouses — of the above "infertile" cohort *at time of treatment.* For women, the only information sought about their partners would be their ages; and

3. offspring born to the identified "infertile" subjects subsequent to their infertility treatment. They would be identified via the Hospital Services Branch (HSB) data file to guarantee the biological relationship.

The three groups identified — the "infertile" cohort, their partners, and their offspring — would then be followed through four data files:

1. the Medical Care Insurance Branch (MCIB) data file contains data on all contacts with physicians (specialists as well as general practitioners) by Saskatchewan residents, including out-of-province consultations. Information is provided on the diagnoses and service associated with each contact. Also included are data on laboratory tests ordered (where available). Since some of the costs of out-of-province IVF treatment are covered, data on the out-of-province IVF treatment of Saskatchewan residents are available from this file;

2. the Saskatchewan Prescription Drug Plan (SPDP) data file records data on all drugs prescribed to individuals normally resident in the province. Prescription drugs are a covered service for all age groups, as part of the comprehensive health care programs available to Saskatchewan residents. Drugs used in out-of-province assisted human reproduction treatment such as IVF are covered by SPDP;

3. the Hospital Services Branch (HSB) data file records data on all hospital separations in the province, including separation date, surgical procedures, length of stay, etc. Information about out-of-province hospitalizations for infertility treatment will also be obtained, where available; and

4. the Saskatchewan Cancer Foundation (SCF) data file contains data on all contacts with physicians for the treatment of cancers.

Searching the MCIB data file would allow us to find both the positive and negative outcomes associated with treatment for infertility — for example, live birth, stillbirth, and further treatment for infertility.

The SPDP data file would provide data on all outpatient prescriptions. Data from this file would allow us to assess total exposure to infertility drug treatment. If adverse effects are found, this should enable us to assess a dose-response relationship. Data available on the use of other "non-infertility" drugs would allow us to assess for both the infertility study cohort and the comparison group, the extent to which the use of these other drugs might be connected to observed adverse birth outcomes, or related to the observed infertility. This data set would also allow us to assess drug use associated with infertility and adverse birth outcomes.

The HSB provides data on hospitalizations including significant events (e.g., live and stillbirths, multiple births, pre-term births, surgical

procedures) occurring during those hospitalizations. These data should provide confirmatory evidence for information on treatment events captured in the MCIB (physician services) data file.

The SCF data file is more than a tumour registry file. The Foundation provides direct services such as radiation and chemotherapies. It also pays for the provision of surgical procedures required to treat neoplasms. This data file would provide information on one general type of negative outcome, cancers, which may be associated with some infertility treatments.

Linkage

In Saskatchewan, because of the use of a unique identifier assigned to each individual covered by the province's health programs, and the use of this number by individuals as they access services, it is possible to link an individual's use of services through time and across service sectors.

Appendix 2 provides a more detailed description of the Saskatchewan health care data files to be used in this study.

Comparison Group

A comparison group of individuals matched for age (±2 years), gender, and residence location would be identified. The postal code would be used for matching on residence location. A 4-digit match would be used for matching subjects residing in the larger cities of Saskatoon, Regina, Moose Jaw, and Prince Albert. A 3-digit match would be sought for all other study subjects. This comparison cohort would be a two-to-one match of the study cohort. The comparison cohort would be identified from the Health Information Registration File (HIRF), which contains identifying information on all individuals resident in the province who are eligible for health services. Information on name, residence, age, marital status, personal health number, family beneficiary number, et cetera, is contained in this data file.

The purpose of the 2× comparison group is to provide base-rate data on the occurrence of the positive and adverse outcomes postulated as being associated with infertility treatment. Since the comparative cohort is a non-treatment group, we can determine to what extent the outcomes observed in the infertility treatment group deviate from the general population (either higher or lower) and thus ascribe that deviation in the occurrence of outcomes to being plausibly an effect of infertility treatment.

It should be noted that, for males, the control subjects would be other males of the same age ±2 years with the same length of health coverage in the province (to within six months) who have not received infertility treatment. For female exposed cohort members who do not become pregnant, the controls would be other females of the same age ±2 years with the same length of health coverage in the province (to within six months) who have not received infertility treatment and who had no pregnancy between 1978 and 1990. For female exposed cohort members who do become preg-

nant, the controls would be other females who have not received infertility treatment and who became pregnant within the same calendar year as the infertility cohort member, are of the same age as the relevant subject ±1.5 years, and who had the same health coverage period (to within six months) as the infertile cohort subject.

Detailed Data Description

A more detailed description of the inception treatment and control cohorts and the data to be collected on each subject is provided in Appendix 1. Monthly health care utilization data would be extracted for six sets of subjects:

1. infertile males;
2. infertile females;
3. offspring;
4. control males;
5. control females; and
6. control offspring.

The Study Data Set

A fixed format data set that contains monthly utilization data for both the "infertile" cohort and the 2× comparison group would be created from data linked together from the MCIB, SPDP, HSB, and HIRF data files of Saskatchewan Health and the Cancer Foundation data file.

This *unified* (linked) *study data set* would be used as the source of data for the study.

Validation

In order to validate the outcome of births, we would need to abstract relevant information from hospital charts and retrieve the birth certificates for all births in both the "infertile" cohort and the 2× comparison group. It is difficult to anticipate the number of records to be abstracted, but it is estimated to be 200 and 400 respectively.

Similar validation would occur for deaths of study subjects. Death certificates and coroner's reports (where available) would need to be retrieved on all deaths involving study subjects. It is difficult at present to estimate the number of such events that would occur in the treatment and control cohorts other than using standard age/sex specific death rates as a guide.

Additional Data Source

It is possible and desirable to use an additional national data source to add information to the data sources currently being used in the study.

In tracking mortality outcomes it would be possible and desirable to make use of the Canadian Mortality Database to determine death for study

subjects, both exposed and control subjects, who may have left Saskatchewan during the study period but who still resided in Canada.

The use of this data source to provide additional data for use in this proposed study, as well as the cost implications of its use, would need to be fully explored.

Data Analysis

In this study, pharmaco-epidemiologic data for an entire population would be examined, rather than a sample of a population. Therefore, trends and variations observed in the data would be statistically "real" rather than a result of sampling variation.

Given the scale of the study, its longitudinal design, and the volume of data to be assembled, a range of data reduction methods would be used to generate patient and prescriber profiles. After these data reduction steps, the analysis of the data would use both exploratory and confirmatory procedures. This part of the analysis would be multi-phasic and employ several different methods. Necessary point prevalence estimates and trends in these estimates for specific sex, age, and residence type groups would be developed. Multivariate methods would be used where appropriate.

Time Frame

A time frame for the proposed project, indicating the major streams and steps in the project, is shown in Figure 1. We have estimated a period of 15 to 18 months to the completion and the writing up of the study's results.

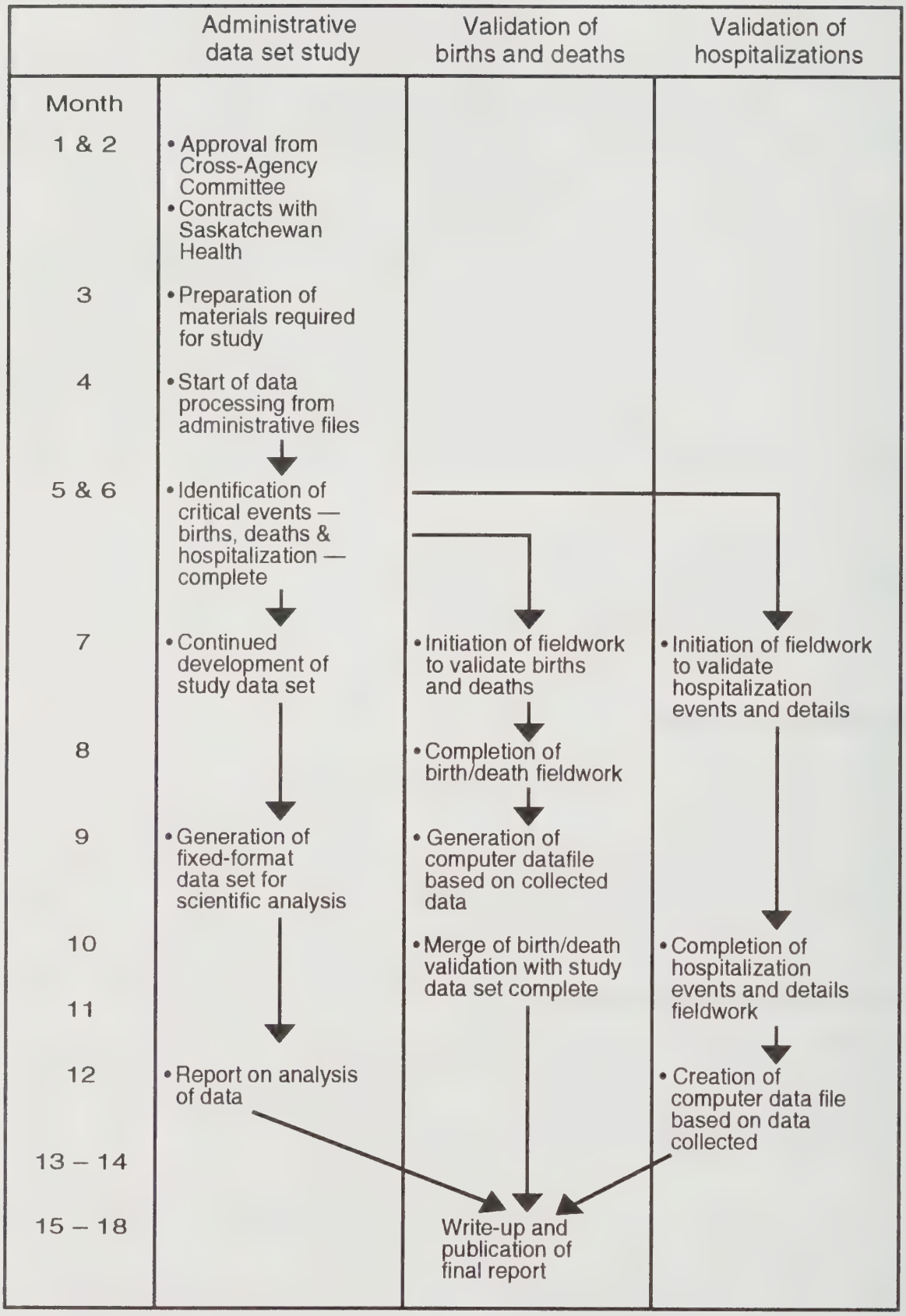
The Research Team

The research should be conducted by a group of researchers familiar with the Saskatchewan health care data files and the health care system in the province. The members of the research team should have complementary research and clinical experience suitable to the proposed project. Team members should have had experience in conducting and completing a wide range of epidemiologic, attitudinal, evaluation and clinical studies. They should be familiar with and have used for research purposes a number of the Saskatchewan health care data files and have a working knowledge of them.

It is suggested that the research team be composed of the following:

- a principal investigator with overall responsibility for the design and execution of the proposed study;
- an epidemiologist/statistician for data analysis, statistical advice, input into study design and the interpretation and writing up of data;
- a medical consultant with experience in obstetrics and gynaecology; and
- a pharmacological consultant.

Figure 1. Time Frames for Proposed Infertility Treatment Study



Proposed Budget

The following would be the approximate budget needed for the proposed study.

1. Personnel *Subtotal = $33 547.00*

a. Professional Services

• Principal investigator	18.5 days @ $500.00 = $9 250.00
• Epidemiologist/ statistician	18.5 days @ $425.00 = $7 862.00
• Medical consultant	6.0 days @ $625.00 = $3 750.00
• Pharmacological consultant	3.0 days @ $425.00 = $1 275.00

b. Technical Services

• Data analyst	55.0 days @ $130.00 = $7 150.00
• Research assistant	22.0 days @ $120.00 = $2 640.00
• Secretarial/clerical	18.0 days @ $ 90.00 = $1 620.00

2. Contracted-out Services *Subtotal = $167 405.00*

To: Pharmacoepidemiology Unit
Laboratory and Disease Control Services
Saskatchewan Health
3211 Albert Street
Regina, Saskatchewan

a.	Project management	$17 400.00
b.	CPU and PA time	$68 150.00
c.	Direct costs of hospital abstracts	$21 750.00
d.	Office fieldwork coordination	$ 7 975.00
e.	Other direct costs (e.g., LD equipment rental)	$ 1 000.00
f.	SCF costs	$ 7 500.00
g.	Administration/professional fee ($75 per hospital abstract)	$30 000.00
h.	Premium for release of data set (20% of b.)	$13 630.00

3. Materials and Supplies *Subtotal = $1 115.00*

a. Office supplies and sundries	$320.00
b. Courier, fax, postage, etc.	$260.00
c. Long-distance telephone	$160.00
d. Computer supplies & sundries	$375.00

4. Travel *Subtotal = $3 990.00*

a. 2 one-person trips Saskatoon/Ottawa return @ $1 550.00 = $3 100.00

b. 2 two-person trips Saskatoon/Regina return (for data acquisition) @ $445.00 each = $890.00

Total Budget Estimate = $206 057.00

Possible Add-on Study

The nature of the data set that would need to be developed for the proposed study would make possible the examination of a different dimension of the infertility problem, namely, the risk of infertility associated with the use (both short-term and prolonged) of particular, specific prescription drugs. In this add-on study, the design would be a large retrospective case cohort and comparison cohort study.

In this subsidiary study we would take the following steps:

1. identify the cohort of *all women aged 25 to 49* in Saskatchewan who have received treatment for infertility during the period *1 January 1986 to 31 December 1990* and *all men also treated* for infertility during this period;
2. identify partners — legal and common-law spouses — of the above infertile cohort at time of treatment; and
3. follow the "infertile" cohort and partners identified in 1 and 2 *backward in time to 1 January 1978.*

The "infertile" cohort and partners would be followed through three data sources:

1. the Saskatchewan Prescription Drug Plan, which would enable us to look at exposure to drugs in general, and more specifically to look at levels of exposure to such drugs as:
   - anti-hypertensive drugs — spironolactone, methyldopa, clonidine, reserpine;
   - barbiturates: sedatives;
   - antidepressants and neuroleptics;
   - cimetidine and ranitidine;
   - propranolol and other β blockers;
   - diazepam (Valium®) and other benzodiazepines;
   - hormonal preparations, including contraceptives; and
   - ergotamine and other anti-migraine drugs;
2. the Medical Care Insurance Branch data file, which contains data on all contacts with physicians (specialists as well as general practitioners) by Saskatchewan residents, including out-of-province consultations, and which also includes data on laboratory tests ordered; and
3. the Hospital Services Branch data file, which contains data on all hospital admissions in the province.

Comparison Group

A 2× comparison group would be identified for this study and traced backwards in time. The data from this 2× comparison group would be analyzed in order to more fully estimate the risk of infertility being associated with any particular drug exposure. The controls would be matched to the subjects on age, sex, and the date on which their health coverage in the province began (to within 6 months).

The Study Data Set

This study will make use of data from the unified study data set identified above. Thus, we would have access to monthly utilization data on physicians' services, hospitalizations, and prescription drug use.

Comment

This additional study could be done for essentially no extra cost. The only extra costs would be those associated with the specific analyses of the unified data set required to answer questions raised in this additional retrospective study.

Potential Problems in Implementing the Study Design

There are four areas in which difficulties would likely have to be overcome in implementing the study design, in terms of using the Saskatchewan health care data files. They are not unique to this province, but would arise in any such study of large data sets. These potential problems areas are the following:

- negotiating adequate access to the required study data;
- dealing with layers of bureaucracy;
- limiting costs; and
- keeping to a manageable time frame.

Obtaining Access to the Data

One of the stumbling blocks in using linked data from the Saskatchewan health care data files has been the insistence of Saskatchewan Health on releasing data required for a study in tabular form only, with the term "study" usually being conceived as a single publishable paper. Saskatchewan Health has stated that this has been necessary in order to ensure client confidentiality and the appropriate use of the data by researchers. However, there are other ways in which the important need to protect privacy can be accomplished. We have felt this approach to the analysis of data is unnecessarily restrictive, expensive, and slow.

While specific tabular output may be acceptable in some studies, for the most part it is inadequate. With such a restrictive process, researchers cannot analyze the data efficiently and with confidence. They are unable to examine the data in a variety of ways, experiment with different categorizations, perform exploratory data analyses, or utilize a variety of statistical techniques to look at the robustness of study results.

For these reasons we have had several discussions with the Pharmacoepidemiology Unit (PU) of Saskatchewan Health aimed at developing better, more timely, and less costly strategies to analyze the health care utilization data. We have been successful in these attempts to protect privacy and improve access to data and have put forward the idea of generating "dummy-identified" fixed-format records on individual cases. The study records would contain health care activity data for a fixed time period - usually a month. It has also been agreed to release the study file so that researchers will be able to perform more comprehensive and thorough analyses as they see fit.

This strategy of a fixed-format study file promises to allow a more flexible and timely process for analyzing project data, as well as reducing the cost of the analysis of that data (but not, of course, reducing the cost of generating the specific study data in the first place).

Limiting Costs

We have generally found that in comparison with other provinces it is expensive to use Saskatchewan health care data for research purposes. At the time of writing, the data sources seem to be viewed by some as a source of potential funds for both the bureaucracy and its private sector computer consultant. The view that these data sources are a valuable asset — a public trust — to be used for the benefit of the population of the province or humankind is lacking. Rather, these data sources (particularly the prescription drug plan data) are seen as commercial products from which substantial revenue can be generated.

The basis on which costs for a particular project are estimated remain mysterious, as they are unarticulated. We are particularly concerned by the lack of "economies of repetition" in obtaining access to Saskatchewan Health data for research studies. We have not seen cost reduction that should, in fact, result from doing various studies with similar data requirements. More recently, another major problem has emerged with respect to data access costs for specific projects, namely, that of substantial cost overruns. In conducting a piece of research, a contract is entered into with the PU for the provision of specific services and data. Unfortunately, the contracts offered to researchers are not fixed price contracts but rather contain estimates on a provision for *actual* charges and cancellation. It is our general experience that costs charged have been substantially more than estimated. The researchers are expected to make up these extra costs. Given the nature of funding for research projects, these additional charges are extremely difficult, if not impossible, to handle and consequently jeopardize the viability of projects. We have been told that the cause of the overexpenditures is inaccurate costing on the part of the computer services company, which is the major supplier of programming services to Saskatchewan Health for research projects involving the health care data bases. The cost overruns have been sufficiently large as to endanger the idea of using these data files for research purposes.

Dealing with the Bureaucracy

In the section on access to the data we noted some problems in getting direct access to appropriately protected, relevant data for which a researcher may have paid a considerable amount of money. There are additional problems posed by having to work through several layers of bureaucracy in dealing with the data.

The PU acts as a buffer between researchers and the private contract computer programmers who actually extract, collate, summarize, and analyze the data. The researchers' requests are translated by the PU staff to the programmers before implementation of the study design takes place. This extra layer seems unnecessary and creates an additional layer of bureaucracy in which communication problems can develop. The presence of this layer also adds to the time required to complete a study. The process is an expensive, cumbersome, and time-consuming way of getting things done.

Keeping to a Manageable Time Frame

It is our experience that the time estimates quoted for studies by the PU and their contract programmers are always far too optimistic.

Given the steps necessary to get approval for a project and the necessity to communicate with project staff of the PU and programmers, it is unlikely that any reasonably large study could be completed in less than 12 months.

In addition, there does not appear to be a queue of studies in which the first in is the first to be dealt with. How the order of priority is determined is unclear.

We estimate that the study outlined in this paper would take 15 to 18 months to complete.

Conclusion

The study outlined in this paper, and the add-on study described, show the kinds of questions that can be answered and the useful information that can be generated using already existing health care files.

This exploration of record-linkage using files that exist in Saskatchewan shows that they can generate scientifically useful information and, as well, have policy significance.

This detailed exploration of a possible study shows the feasibility of this kind of approach, and should encourage investigators to pursue this line of research with regard to infertility, its causes, and treatment outcomes.

Appendix 1. Description of Patient File for RCNRT Studies — Monthly Utilization Record

The following is a general description of the data required for this project.

1. Both studies use the same data file, which is referred to as the unified study data set in the project proposal. The file covers the years 1978-1990. A dummy identifier will be used to uniquely identify each individual while protecting his or her true identity from the researchers. Registered Indians will be omitted from this study. Each 'case' will be treated independently, and if both partners in a relationship are receiving infertility treatment, they will both be included in the study as separate individuals cross-referenced to each other.

2. 'Case' individuals are selected primarily on ICD infertility codes 606 (males) and 628 (females) in the MCIB file, but certain procedure codes will also be used to identify them. These codes are as follows:

(a)	ovulation induction IV/IM injections	110A
(b)	hydrotubation	36P
(c)	salpingostomy	236P/237P
(d)	tubo-uterine implantation	137P
(e)	reanastomosis of fallopian tubes	141P
(f)	gonadotropin therapy	314P/315P
(g)	utero-salpingogram	244X
(h)	sperm washing prior to insemination	338P
(i)	seminal fluid analysis	35R
(j)	vaginal sperm examination	30P
(k)	tubal insufflation	31P
(l)	artificial insemination	108P

Cases will also be identified from procedures/diagnoses for hospital admissions relating to infertility. The ICD codes will be the same (i.e., 606 and 628). The procedure codes are listed as follows:

(a)	excision of varicocele and hydrocele of spermatic cord	75.0
(b)	excision of cyst of epididymis	75.1
(c)	excision of other lesion or tissue of spermatic cord	75.2

(d)	repair of spermatic cord and epididymis	75.4
(e)	vasotomy	75.5
(f)	repair of vas deferens and epididymis	75.7
(g)	invasive diagnostic procedure on spermatic cord, epididymis, or vas deferens	75.8
(h)	repair of ovary	77.6
(i)	salpingotomy	78.0
(j)	repair of fallopian tube	78.6
(k)	insufflation of fallopian tube	78.7
(l)	repair of internal cervical os	79.4
(m)	repair of uterus	81.5
(n)	artificial insemination	81.92

In addition, the use of selected drugs in the SPDP data file will be a cohort identifier. These drugs are the following:

Females	**Males**
menotropins (hMG)(Pergonal®)	menotropins (hMG)
chorionic gonadotropin (hCG)	chorionic gonadotropin (hCG)
bromocriptine	bromocriptine
pure follicle-stimulating hormone (FSH)	tamoxifen
clomiphene	
urofollitropins	
Danazol®	

3. The selected individuals must be aged 25 or older for men, and between 25 and 49 (inclusive) for women. Note that the follow-up for women in their 40s will extend beyond the age of 49. Once an individual is identified, that person's legal or common-law spouse at the time of the treatment is to be identified. For an identified woman, all that will be taken from her partner's file is his age. In addition, any offspring subsequent to their infertility treatment are to be identified. It should be noted that there may be some instances where both the male and the female in the partnership are included as cases and will be counted independently.

4. For each identified person, we require the following:

   (a) A unique identifier;

(b) The following sociodemographic data about the case based on year of index event (from December of that year):

- age;
- sex;
- residence location (city/town/village/rural municipality and north);
- family size at time of index event; and
- spousal information — if the case is a woman, we require the age and HIRF identifier of the male partner; if the case is a man, we require the age and HIRF identifier of the woman and details of any pregnancy (limited to the first five) and the children produced, as specified below.

(c) The following details of the index event (these all refer to the experience of the case or matched control individual):

(i) from MCIB:

- date of index event;
- diagnosis code;
- type of physician (GP, obstetrician/gynaecologist, other specialist); and
- procedure.

(ii) from SPDP:

- date of prescription;
- drug name or code;
- quantity and strength of drug prescribed; and
- prescriber type (GP, obstetrician/gynaecologist, other).

(iii) from HSB:

- date of admission;
- primary and secondary diagnosis;
- procedure; and
- physician type (GP, obstetrician/gynaecologist, other).

The case experience from one of the three data sources — MCIB, SPDP, or HSB — must be the index event, but it is possible that more than one of these events may occur on the same date.

(d) The 30-day-period service utilization for each period for the years 1978-1990, for a maximum of 9 years or to death or migration if earlier; this will include the period number, as well as the following:

(i) from MCIB, diagnoses and procedure codes that relate to the following events:

- pregnancy (up to five events in each category; flag if more):
  - — pregnancy with abortive outcome (ICD-9: 630-639);
  - — complications mainly related to pregnancy (ICD-9: 640-648, except 643 and 647);
  - — normal delivery and other indications for care in pregnancy, labour and delivery (ICD-9: 650-659);
  - — complications occurring mainly in the course of labour and delivery (ICD-9: 660-669); and
  - — complications of the puerperium (ICD-9: 670-676).

(NB: The information in this section is about the case if it is a woman, and about the spouse if the case is a man.)

- congenital abnormalities (ICD-9: 740-759); and
- conditions originating in the perinatal period (ICD-9: 760-779).

(NB: The information for the previous two items is about any offspring regardless of the sex of the case.)

- Infertility:
  - — further treatment of the type specified in the identification section administered to the case; and
- endometriosis (ICD-9: 617) and disorders of menstruation and other abnormal bleeding (ICD-9: 626) — only to be completed if the case is a woman.

(ii) from SPDP, information on prescriptions for drugs dispensed to the case (including quantity and strength), defined in the identifying section and categorized as follows:

- anti-infectives (08:00);
- cardiovascular drugs — subgrouped as in the Saskatchewan Formulary;

- NSAIDs (28:08.04);
- other analgesics (28:08.08, 28:08.12, 28:08.92);
- anti-convulsants (barbiturates) (28:12.04);
- anti-convulsants (benzodiazepines) (28:12.08);
- anti-convulsants (hydantoins) (28:12.12);
- anti-convulsants (miscellaneous) (28:12.92);
- anti-depressants (28:16.04);
- tranquillizers (28:16.08);
- anxiolytics, sedatives, and hypnotics (barbiturates) (28:24.04);
- anxiolytics, sedatives, and hypnotics (benzodiazepines) (28:24.08) — divided into short-acting and long-acting;
- anxiolytics, sedatives, and hypnotics (miscellaneous) (28:24.92);
- lithium (28:28.00);
- diuretics (40:28.00);
- potassium-sparing diuretics (40:28.10);
- H_2 antagonists;
- other GI drugs (56:00);
- hormones and substitutes (68:00) — individually identified, except anti-diabetic products;
- anti-migraine drugs (12:16);
- bromocriptine;
- clomiphene;
- other Formulary drugs; and
- EDS drugs suitably categorized (e.g., anti-infective EDS is to be put with anti-infectives).

(iii) from SHSB, diagnoses and procedure codes that relate to the following:

- pregnancy;
- congenital abnormalities and conditions originating in the perinatal period;
- infertility, as defined above

- details about the admission — e.g., length of stay, physician/surgeon type — as requested from the MCIB above; and
- numbers of psychiatric (defined as any admission with an ICD psychiatric diagnosis) and other hospitalizations experienced by the case during the period.

(iv) from SCF, the following events:

- malignant neoplasms suffered by the case (these should be "new" diagnoses); and
- diagnoses of and treatment for cancer (ovarian/breast/endometrium/other) in the identified individuals: for men, the code will be new cancer or not; for women, new ovarian cancer (y/n), new breast cancer (y/n), new endometrium cancer (y/n), new other type of cancer (y/n).

(e) For each case individual, a "control" individual will be identified as follows:

- for female cases who become pregnant, a female not on infertility treatment who became "pregnant" (identified by suitable code from MCIB) within the same year, whose age is ±2 years of the case age, and who has the same length of medical coverage in the province (to within six months) as the case has, following infertility treatment;
- for female cases who do not become pregnant, a female not on infertility treatment whose age is ±2 years of the case age, who has the same length of medical coverage in the province (to within six months) as the case has, following infertility treatment, and who had no pregnancy in the period 1978-1990;
- for males, a male not on infertility treatment whose age is ±2 years of the case age and who has the same coverage in the province (to within six months) as the case has, following infertility treatment; and
- the same information described in (d) above for the controls, who should be followed for up to nine years, or until death or migration, as far as the year 1990.

(f) An indicator as to whether the person died or moved out of the province before the end of the nine-year follow-up, or

was present throughout; also, the date of the end of the follow-up period.

(g) A summary of the direct costs incurred by the subject in the various treatment sectors on a monthly basis:

- total dollars prescription drugs;
- total dollars physician services; and
- total dollars hospital services.

5. For those individuals identified as receiving first infertility treatment during the period 1986-1990 inclusive, we also require the following information on a 30-day-period basis backward in time for five years, or the date of the initiation of health care coverage, or to January 1978, whichever is first encountered (NB: the file should include the date of the start of the period examined):

- information on medications from the SPDP (using the above categorization);
- information from MCIB on tubal ligations (135P) and re-anastomosis (141P), vasectomies (190R), and reanastomosis of vas deferens with intra-luminal splinting (191R), inflammatory diseases of the female pelvic organs (ICD-9: 614-616), gonorrhoea (ICD-9: 098), and endometriosis (ICD-9: 617);
- information from HSB on tubal ligations (78.53) and reanastomosis (78.6), vasectomies (75.6) and repair of vas deferens (75.7), inflammatory diseases of the female pelvic organs (ICD-9: 614-616), gonorrhoea (ICD-9: 098), and endometriosis (ICD-9: 617); information on pituitary tumours (ICD-9: 194.3, 227.3, and 237.0);
- information from SCF on prior cancer, particularly endometrial cancer in women; the first occurrence (i.e., diagnosis or notification to SCF) of any cancer in males and either endometrial or "other" in females; and

  For this part of the study, we will require different control individuals. The controls will be matched on age (within same index year), sex, and service initiation date (this must be within six months of case initiation). The same information will be required for the controls, as described above, backward in time for five years, or to their initiation date or January 1978, whichever is found first.

6. A similar detailed file description is required for offspring. Because the focus of the study for live births is somewhat different, the precise content of the data file will be somewhat

different than that above; however, the above file description gives a very good idea of the nature and structure of that data.

Appendix 2. The Data Files to Be Used in the Proposed Study

The study will use the health care utilization data files of the following branches of Saskatchewan Health, the provincial health department.

The Health Insurance Registration File (HIRF)

The HIRF contains the identification and demographic details of all residents eligible for Saskatchewan Health services. It is the central data file of the whole system and is used by all branches except the Vital Statistics Branch. Approximately 95% of the Saskatchewan population is eligible for health benefits. Ineligible individuals are those whose health care is federally funded; they include members of the Canadian Armed Forces and the RCMP, and inmates of federal penitentiaries.

All Saskatchewan residents eligible for health benefits (known as the "covered population") are assigned a unique identifier which is recorded in the HIRF and is used when obtaining health services. Although an individual's identifier might change under certain circumstances, such as a change in family status, a mechanism exists within the system that allows for continuous linkage of each person, thus eliminating loss to follow-up for longitudinal studies. The same linking mechanism is used when a resident leaves the province but returns to take up residence some years later.

The HIRF is updated daily and is verified through continuous routine checks. The file captures the following data on every member of the covered population: name; unique identifier; sex; marital status; month and year of birth; dates of health coverage eligibility; date of death (if applicable); mailing address; residence code; an indicator for Registered Indian status; and an indicator for a current recipient of the Saskatchewan Assistance Plan.

The Hospital Services Branch (HSB)

The HSB administers the Hospital Services Plan under which the 134 provincial hospitals supply services without charge to all members of the covered population and, in doing so, it collects data on acute care inpatient separations, day surgery, and out-of-province separations involving members of the covered population. The information in the SHSB data file includes: diagnostic and treatment data (up to two discharge diagnoses coded using ICD, and procedures coded using the Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures); separation data (date of separation, length of stay, etc.); and physician data (a code for the

physician, which can be linked to a file giving the specialty, date of graduation; and other details concerning the physician).

The Medical Care Insurance Branch (MCIB)

The MCIB deals with all matters relating to the payment for physician services and is the custodian of the physician services data files that contain information on the patient, the physician, the service provided, and a diagnosis coded using ICD.

The Prescription Drug Services Branch (PDSB)

The PDSB administers the SPDP, which provides outpatient prescription drug coverage to all members of the covered population, except those whose prescription costs are paid by another government agency. The latter include persons whose drug services are funded by National Health and Welfare (Registered Indians), the Workers' Compensation Board, and Veterans Affairs Canada. The exclusions account for about 6% of the provincial population.

All drugs given general coverage under the SPDP are listed in the Saskatchewan Formulary. The Formulary places some limitations on the drugs given financial coverage, although any drug licensed in Canada may still be prescribed in the province. The Formulary is not as limited as hospital formularies often are. Information in the PDSB data file includes: patient data; drug data (drug identification number, active ingredient number, generic and brand names, manufacturer, date, and quantity dispensed); prescriber data; and cost data.

For the purposes of epidemiologic research there have been three distinct phases in the general SPDP program since it began in September 1975. Each of these phases was characterized by a different reimbursement scheme (passive, active, and passive again) and levels of deductibles and co-payment. The available data can be summarized as follows:

1. complete data on Formulary drugs are available from September 1975 to June 1987, during which time over 51.5 million prescription claims were submitted to the PDSB (Strand and West 1989);
2. some drug data are available for the period between July 1987 and December 1988 but, in general, since the data were not collected on an individual basis but by family unit, information from this period is of little use for pharmaco-epidemiologic research; and
3. from 1989 onwards, complete data on Formulary drugs prescribed to individuals again became available.

There are limitations on the numbers of drugs given general coverage under the SPDP (Rawson 1992a, 1992b) in that every brand of a drug may not be covered. In addition, since some drugs may be approved for

marketing in Canada later than in other industrialized countries and coverage under the SPDP can only take place after federal approval, a drug may achieve widespread use in the province later than elsewhere (Rawson 1992a). Nevertheless, as Table 1 in the text of the proposal demonstrates, most popular drugs used to assist the human reproductive process are currently covered by the Saskatchewan Prescription Drug Plan.

The ability to link data from the Saskatchewan health care files successfully and usefully has been demonstrated by D'Arcy et al. (1976). The information has been used in a variety of investigations ranging from relatively simple studies using single data files (West et al. 1985; Theissen et al. 1990), through studies linking two files, to complex studies combining information from several files (Ray et al. 1989; Horwitz et al. 1991). Most recently, the data files have been used to address such important problems as: gastrointestinal haemorrhage following the use of non-steroidal anti-inflammatory drugs (Guess et al. 1988); the occurrence of depression following the use of β-blockers (Theissen et al. 1990); and the use of β-agonists, and the risk of death or near-death among asthmatics (Spitzer et al. 1992; Horwitz et al. 1991). The reports from these studies have been published in quality national and international journals.

Other work using the linked provincial health care data files is in progress, including studies of the utilization of psychoactive drugs, an assessment of the potential of the files as a resource for an Adverse Drug Reaction alerting system, and an investigation of the reliability of the information in the data files.

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Mandate

(approved by Her Excellency the Governor General
on the 25th day of October, 1989)

The Committee of the Privy Council, on the recommendation of the Prime Minister, advise that a Commission do issue under Part I of the Inquiries Act and under the Great Seal of Canada appointing The Royal Commission on New Reproductive Technologies to inquire into and report on current and potential medical and scientific developments related to new reproductive technologies, considering in particular their social, ethical, health, research, legal and economic implications and the public interest, recommending what policies and safeguards should be applied, and examining in particular,

(a) implications of new reproductive technologies for women's reproductive health and well-being;

(b) the causes, treatment and prevention of male and female infertility;

(c) reversals of sterilization procedures, artificial insemination, *in vitro* fertilization, embryo transfers, prenatal screening and diagnostic techniques, genetic manipulation and therapeutic interventions to correct genetic anomalies, sex selection techniques, embryo experimentation and fetal tissue transplants;

(d) social and legal arrangements, such as surrogate childbearing, judicial interventions during gestation and birth, and "ownership" of ova, sperm, embryos and fetal tissue;

(e) the status and rights of people using or contributing to reproductive services, such as access to procedures, "rights" to parenthood, informed consent, status of gamete donors and confidentiality, and the impact of these services on all concerned parties, particularly the children; and

(f) the economic ramifications of these technologies, such as the commercial marketing of ova, sperm and embryos, the application of patent law, and the funding of research and procedures including infertility treatment.

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